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## Original Communications

# THE TREATMENT OF ACUTE RESPIRATORY INFECTIONS IN CHILDREN WITH ORALLY ADMINISTERED, UNBUFFERED PENICILLIN SOLUTIONS

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CHICAGO, ILL.

THE efficacy of orally administered penicillin in the treatment of acute infections produced by susceptible organisms is now firmly established. It is true that some of the administered penicillin is destroyed by gastric juice and that another portion may be destroyed by bacteria before it can be absorbed, but it has been demonstrated by us[1, 2] and by others,[3, 4] that if oral doses of 100,000 units every three hours are used for adults, effective plasma penicillin levels will be achieved comparable with those obtained with intramuscular injections of 20,000 units every three hours. Such a dosage schedule, especially if preceded by a priming dose of 200,000 units, has been found to be therapeutically effective in the management of lobar pneumonia and other acute infections in adults. Moreover, these investigations have thrown doubt on the necessity of buffering agents to prevent the destruction of penicillin by gastric hydrochloric acid. Practically as good plasma levels and as good therapeutic results have been obtained with penicillin prepared in capsules without buffers as with such protective agents.

In the treatment of acute respiratory infections in children, oral penicillin is being widely used. However, because there have been few investigations of the proper dosage for the various age groups, many physicians have reserved the oral medication for the convalescent period, utilizing either parenterally injected penicillin or sulfa drugs for the severe phase. The dosage schedules have been empirical and haphazard, and no correlation has been ascertained between age or weight and the dose required to produce effective plasma penicillin levels. Ross and co-workers[4] have obtained good results in the treatment of pneumonia in children but give no data for the establishment of the proper dosage. Buchanan[5] has studied the plasma penicillin levels following oral administration to infants below 6 months of age, but has offered no comparable information on older age groups nor any clinical confirmation.

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Aided by a grant from Commercial Solvents Corporation.
*Medical director, LaRabida Jackson Park Sanitarium, and Fellow, Hektoen Institute for Medical Research.

The present investigation was undertaken to determine first what dose of oral penicillin administered in aqueous solution without buffers was required in order to achieve therapeutic levels in infants and children of varying ages and sizes, and second, whether therapeutic management based on the results of these assays would be satisfactory.

## METHODS

The penicillin used in these studies was in the form of soluble tablets of crystalline potassium penicillin containing no excipient.* These tablets assayed 50,000 units per tablet. They dissolved readily in water and had none of the mouldy taste of impure penicillin fractions. The solution had the slightly bitter taste generally found in potassium salts but this could easily be masked with sugar, syrups, or saccharin. In this study, the material was dissolved in a 20 per cent Cartose† solution in a dilution of 20,000 units per 4 c.c. The solutions were colored with a vegetable dye to allow recognition of regurgitation of the medicament if that occurred. For the assays the doses were accurately measured from pipettes. In the later therapeutic studies, the three-hourly dose was dispensed from measuring glasses by the ward nurses who were instructed to make the measurements as accurate as possible. For infants under 1 year of age the medicament was prepared as a sterile solution and administered by dropper. It was not considered advisable to administer the penicillin in the milk formula. The stock penicillin solution was kept in the refrigerator between doses and was discarded at the end of two days. Analyses of these solutions revealed stability of the penicillin for at least two days.

Estimation of plasma penicillin was made by the Hickey[6] modification of the Randall, Price, and Welch[7] serial dilution method in which *Bacillus subtilis* (NRRL B-558) was utilized. Blood specimens were drawn during the forenoon and early afternoon, were mixed with citrate, and stored in the refrigerator until late in the afternoon when the serial dilutions were prepared. Three serial dilutions of standard penicillin solution in phosphate buffer were run with each daily batch of plasma specimens. The tubes were incubated at 32° C. for sixteen to seventeen hours.

As shown in previous studies[1, 2] there was no evidence of any appreciable nonspecific inhibition of *B.* subtilis growth in our plasma samples. In one hundred and twenty samples of penicillin-free plasma, only one showed nonspecific inhibition of *B. subtilis* growth; this was equivalent to 0.03 units per cubic centimeter. In more recent studies, to be published, in 100 samples of plasma of relatively high penicillin concentration, the values found after treatment with adequate quantities of penicillinase were always zero. These findings, in addition to the many hundreds of zero penicillin levels in our assays when such levels were expected, have convinced us that at least in our hands, the *B. subtilis* method is reliable and can be utilized without penicillinase controls with each determination.

The assays on the infants and children were performed by the determination of the plasma penicillin levels one and three hours after a test dose of penicillin.

*The tablets were kindly supplied by Commercial Solvents Corporation. The manufacturer reports that over 95 per cent of the product is potassium penicillin G. It assayed 1,500 units per milligram.

†Furnished by H. W. Kinney & Sons, Inc.

An hour before the test dose, a priming dose of twice the quantity of the test dose was administered. Such a method of assay has been found by us as most likely to give the same plasma level as when the dose has been given therapeutically every three hours for one or more days. The priming dose was given at 9 A.M., the assay dose at 10 A.M.; blood was drawn at 11 A.M. and 1 P.M. Though the older children could undoubtedly have taken the tablets either sublingually or perorally, the penicillin was offered to all children both in the assays and the therapeutic studies in the form of solution, so that all results would be comparable. The infants and children chosen for the assays were hospital boarders or patients convalescent from acute illness or those with chronic ailments that did not involve the heart, circulation, or kidneys.

## RESULTS OF ASSAYS

Tables I and II give a summary of the assays of plasma penicillin levels made in 209 infants and children. The size of the test done for each age group was determined empirically after a few preliminary trials. The averages shown in the tables are modified geometric means which have been shown in our previous studies to give less exaggerated significance to occasional unusually high plasma penicillin levels than do arithmetical means. To obtain this mean value, each penicillin level was given a linear weighting, 1 for levels below 0.031 units per cubic centimeter, 2 for 0.031, 3 for 0.062, 4 for 0.125, etc. The arithmetical mean for these weightings was calculated, and the value obtained was translated back into units per cubic centimeter. The fractional portion was extrapolated arithmetically.

Table I shows that it was possible to obtain prolonged high plasma penicillin concentrations in infants below one year of age with doses of 10,000 to 20,000 units. For 20,000 units, the average levels at one hour and three hours respectively were 1.10 and 0.48 unit per cubic centimeter. Even with 10,000 units, which per kilogram was approximately 0.90 and 0.32 for the one- and three-

TABLE I. FREQUENCY DISTRIBUTION OF PLASMA PENICILLIN LEVELS IN 70 INFANTS ADMINISTERED POTASSIUM PENICILLIN IN AQUEOUS SOLUTION BY MOUTH*

| WEIGHTED VALUE | PLASMA PENICILLIN U/C.C. | AGE AND DOSAGE UNITS | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0-3 MO. 10,000 UNITS | | 0-3 MO. 20,000 UNITS | | 3-6 MO. 15,000 UNITS | | 3-6 MO. 20,000 UNITS | | 6-12 MO. 20,000 UNITS | |
| | | 1 HR. | 3 HR. | 1 HR. | 3 HR. | 1 HR. | 3 HR. | 1 HR. | 3 HR. | 1 HR. | 3 HR. |
| | 0 | | | | | | | | | | |
| 1 | (0.03) | | | | | | | | | | |
| 2 | 0.03 | | | | | | 1 | | | 1 | 6 |
| 3 | 0.06 | | 1 | | 1 | 1 | 2 | | 2 | | 7 |
| 4 | 0.125 | | 1 | | 1 | 1 | 3 | 1 | 2 | 7 | 9 |
| 5 | 0.25 | 1 | 9 | 1 | 2 | 3 | 3 | | | 11 | 3 |
| 6 | 0.50 | 6 | 1 | 3 | 1 | 4 | 2 | 1 | | 5 | 1 |
| 7 | 1.0 | 6 | 3 | 2 | 4 | 3 | 1 | 3 | 1 | 3 | 1 |
| 8 | 2.0 | 2 | | 3 | 1 | | | | | | 1 |
| 9 | 4.0 | | | | | | | | | | |
| 10 | 8.0 | | | 1 | | | | | | 1 | |
| Total cases | | 15 | 15 | 10 | 10 | 12 | 12 | 5 | 5 | 28 | 28 |
| Modified geometric average—U/c.c. | | 0.90 | 0.32 | 1.10 | 0.48 | 0.40 | 0.19 | 0.60 | 0.15 | 0.30 | 0.11 |
| Average weight of subjects (kg.) | | | | 3.95 | | | 6.00 | | | 6.86 | |

*The assay dose was preceded in 1 hour by a priming dose of twice the quantity.

TABLE II. FREQUENCY DISTRIBUTION OF PLASMA PENICILLIN IN 139 CHILDREN 1 TO 12 YEARS OLD ADMINISTERED CRYSTALLINE POTASSIUM PENICILLIN IN AQUEOUS SOLUTION BY MOUTH*

| WEIGHTED VALUE | PLASMA PENICILLIN U./C.C. | AGE AND DOSAGE | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1-4 YR. 40,000 UNITS | | 4-6 YR. 50,000 UNITS | | 4-6 YR. 60,000 UNITS | | 6-10 YR. 60,000 UNITS | | 6-10 YR. 80,000 UNITS | | 10-12 YR. 80,000 UNITS | | 10-12 YR. 100,000 UNITS | |
| | | 1 HR. | 3 HR. | 1 HR. | 3 HR. | 1 HR. | 3 HR. | 1 HR. | 3 HR. | 1 HR. | 3 HR. | 1 HR. | 3 HR. | 1 HR. | 3 HR. |
| | 0 | | | | | | | | | | | | | | |
| 1 | (0.03) | 1 | 9 | | 4 | | 3 | 2 | 4 | 1 | 11 | 1 | 4 | | 6 |
| 2 | 0.03 | 5 | 6 | 1 | 2 | 2 | 12 | 3 | 4 | 5 | 10 | 3 | 5 | | 7 |
| 3 | 0.06 | 6 | 8 | 4 | 2 | 8 | 5 | 3 | 3 | 10 | 11 | 3 | 2 | 7 | 3 |
| 4 | 0.125 | 7 | 3 | 4 | 1 | 9 | 1 | 2 | 1 | 12 | 3 | 2 | | 7 | 2 |
| 5 | 0.25 | 5 | 2 | 1 | 2 | 3 | 1 | 2 | | 8 | 1 | 1 | | 3 | |
| 6 | 0.50 | 3 | | 1 | | | | | | | | | | 1 | |
| 7 | 1.0 | 1 | 1 | | | | | | | | | 1 | | | |
| 8 | 2.0 | 1 | | | | | | | | | | | | | |
| Total cases | | 29 | 29 | 11 | 11 | 22 | 20 | 12 | 12 | 36 | 36 | 11 | 11 | 18 | 18 |
| Modified geometric average—U/c.c. | | 0.12 | 0.05 | 0.11 | 0.05 | 0.10 | 0.04 | 0.06 | 0.03 | 0.10 | 0.05 | 0.08 | 0.025 | 0.12 | 0.03 |
| Average weight of subjects (kg.) | | 11.44 | | 17.98 | | | | 26.01 | | | | 33.82 | | | |

*The assay dose was preceded in 1 hour by a priming dose of twice the quantity.

hour interval. With increasing age the infants showed lower values; nevertheless, those from 6 to 12 months showed higher levels than older children. It will be noticed, too, that the high levels found in these infants were well maintained for the three hours. There were no instances of zero levels and only an occasional 0.03 value. Often the concentration at three hours was as high as 1.0 unit per cubic centimeter. Similar findings for young infants recently have been reported by Buchanan.[5]

In children ranging from 1 to 12 years, approximately the same average plasma penicillin levels were obtained in all the age groups, if the test dose was made on the basis of the average weight for the group (see Table II). The average levels at one hour ranged between 0.10 and 0.12 unit per cubic centimeter, while at three hours it ranged between 0.03 and 0.05 unit per cubic centimeter. On the basis of the efficacy of 20,000 units intramuscularly every three hours in adults, satisfactory therapeutic results in most acute infections produced by sensitive organisms can be expected if the plasma penicillin concentration is at least 0.03 unit per cubic centimeter all of the time and greater than 0.06 most of the time. Therefore, the levels obtained in these assays on doses which approximated 3,000 units per kilogram (or 1,400 units per pound) can be regarded as therapeutically satisfactory.

From Table II it can be seen that smaller doses, 60,000 units instead of 80,000 units for the 6- to 10-year group and 80,000 units instead of 100,000 for the 10- to 12-year group, gave relatively unsatisfactory results. It will also be noted that the dosage required for the 10- to 12-year group is that which we[1] found to be necessary for adults, namely 100,000 units.

The inordinately high levels achieved in the young infants are probably related to the relatively poor renal function found normally in these infants. McCance[6] has shown that urea clearance is markedly low in the newborn infant

and does not approach the values of adults until well after seven months. Our own studies of premature and full-term newborn infants[9] have given similar findings. The normal infant, like the adult nephritic, is unable to concentrate the urine. That the high penicillin levels were not due to too rapid absorption from the intestinal tract is indicated by the fact that the levels at three hours were still quite high, much higher than is seen after parenteral injections of comparable doses in adults.

## THERAPEUTIC STUDY

For a study of the efficacy of orally administered penicillin in acute respiratory infections in children, advantage was taken of the moderately severe epidemic of such infections that took place between February and April, of 1947. The aim was to treat all patients admitted for acute respiratory infections to the Children's Division of the Cook County Hospital during the one continuous period of the epidemic. Since most of the admissions were at night, the resident in the admitting room was called upon to make the diagnosis and initiate the treatment. For the first two weeks of the study, these residents, previously unconvinced of the efficacy of oral penicillin, tended to select only patients with mild upper respiratory infections for the oral therapy and to reserve the severe cases for parenteral penicillin or for sulfa therapy. Such a procedure allowed the inclusion of obvious virus infections in the group. To obviate this tendency, it was made mandatory that the resident place all patients with rectal temperatures higher than 100° F. on the oral medication. A much better choice of cases was thereby effected. The resident was asked to obtain a throat and gag bacteriological specimen for culture at the time of the admission of the patient and to place the swab in a sterile tube containing 2 c.c. of sterile saline solution. These were placed in the refrigerator until picked up by the technicians at 9 A.M. (or during the day for day admissions) and streaked on blood agar plates.

Colonies appearing like $\beta$-hemolytic streptococci and pneumococci after sixteen to twenty-four hours incubation were isolated and subcultured on blood agar slants. These were identified by Gram stain and by bile solubility tests. The pneumococci were typed by the Neufeld technique.

The penicillin was administered as for the assays in a 20 per cent Cartose solution. The dosage per three hours used was on the basis of age according to the following scheme as evolved from the assays: 0 to 1 year, 20,000 units; 1 to 4 years, 40,000 units; 4 to 6 years, 60,000 units; 6 to 10 years, 80,000 units; 10 to 12 years, 100,000 units. A priming dose equal to twice the therapeutic dose was given immediately to the patient, who was then placed on the regular dosage on a 3, 6, 9, and 12 o'clock schedule. Blood specimens were drawn at least once, usually at three hours after a 9 A.M. dose, and analyzed for penicillin. White cell counts were made within the first twenty-four hours.

## RESULTS OF TREATMENT

It was decided to use as a criterion for the cases to be included in the evaluation of penicillin therapy an initial temperature of over 100° F. and an admission diagnosis of respiratory infection uncomplicated by other recognizable diseases producing fever. On this basis, of the 168 patients treated with the

oral preparation of crystalline potassium penicillin, twenty were discarded because of low initial temperatures and/or indefinite diagnosis. Most of these probably had common colds. In addition, there was one case of each of the following: measles, pertussis, infectious mononucleosis, congenital syphilis, and rheumatic fever. These five cases were also discarded, leaving 143 cases for analysis.

The therapeutic results in these 143 cases were not always easy to evaluate. It was recognized that the study was conducted during a moderately severe and widely disseminated influenza epidemic and that many of the infections were primarily of virus origin or were bacterial involvements complicated with a virus component. Small children even with common cold often have high temperatures for the first or second day of the illness which may subside spontaneously or with aspirin. (For this reason, aspirin medication was forbidden in these cases.) When the response is due to penicillin, the temperature usually stays down unless an accompanying virus infection still persists. Bacterial infections that respond to penicillin usually show white cell counts above 9,000 per cubic millimeter, but it is well known that this criterion is not infallible. It should also be remembered that while the finding of a specific and a potentially pathogenic bacterium is usually indicative of a bacterial infection, this may not necessarily be the case. The bacteria may be either only secondary invaders or nonparticipants in the infection.

With these difficulties in mind the therapeutic results were set up in three categories:

*Good results:* The rectal temperature dropped to 99.6° F. within forty-eight hours and remained so for at least twenty-four hours; the clinical condition improved correspondingly.

*Fair result:* The patient felt better, but the temperature did not fall to normal until after forty-eight hours but did so during the penicillin medication within four days.

*Poor results:* The patient's temperature and clinical condition did not return to normal within four days, and the medication had to be changed to parenteral penicillin or sulfadiazine.

Of the 143 cases used for evaluation, there were good results in ninety-four, or 65.7 per cent; fair results in twenty-six, or 16.1 per cent (see Table III-A). There were no deaths. However, it is obvious that patients moribund on admission could not be placed on the oral management. In a number of instances of poor results, the patients showed no better response with sulfadiazine or parenteral penicillin. These were probably cases of virus infections. Thus a satisfactory clinical response to oral penicillin was obtained in 84 per cent of the patients. One of the indications of the effectiveness of the therapy was the enthusiasm for this therapy that developed among the previously skeptical residents as the study continued.

To determine whether those patients in whom positive bacterial cultures were obtained showed better results than the group as a whole, the seventy-three of such cases were similarly evaluated. The results shown in Table III-B show an insignificant improvement in the good and fair groups, 68.5 and 17.8 per

TABLE III

| GROUP | RESULTS | | | | | | TOTAL |
|---|---|---|---|---|---|---|---|
| | GOOD | | FAIR | | POOR | | |
| | NO. | % | NO. | % | NO. | % | |
| A. No. patients studied (excluding five with specific diseases) | 94 | (65.7) | 26 | (18.2) | 23 | (16.1) | 141 |
| B. No. patients with positive bacteriological cultures | 50 | (68.5) | 13 | (17.8) | 10 | (13.7) | 73 |
| C. No. patients with white blood cell count of 9,000 or over | 62 | (68.1) | 15 | (16.5) | 14 | (15.4) | 91 |

cent respectively, the poor results dropping slightly to 13.7 per cent. Again, if the ninety-one patients whose white cell counts were higher than 9,000 are similarly evaluated, the results are negligibly altered. (See Table III-C.) Thus it was not found possible to ascribe the poor results in the 15 per cent or so of cases to the presence of an accompanying virus infection. Yet our clinical and epidemiological experience would make us feel that such was the case.

The plasma penicillin levels were determined at the three-hour interval in 115 patients. More plasma levels at other intervals would have been desirable but were not feasible. The frequency distributions, shown in Table IV, indicate that on the whole the dosages were adequate to produce a sustained therapeutic level. There were only fifteen zero levels (that is, less than 0.03 unit per cubic centimeter). This amounts to 13.1 per cent. The modified geometric average for all age groups was about 0.06 unit per cubic centimeter for all ages above 1 year and 0.10 for those under 1 year of age. These levels at three hours are of the same order as those found in the assays. As in the assays, the patients in the 10- to 12-year group showed slightly lower penicillin levels at three hours, even though on a dosage equal to that given adults. With the assays as a gauge, it is almost certain that the levels at one hour were of the order of 0.125 cubic centimeter. Such concentrations of penicillin have previously been found therapeutically effective, and the present clinical results are in keeping with these findings.

Table V shows the distribution of plasma penicillin levels on the basis of good, fair, and poor clinical results. There appeared to be no significant differences in the averages in the three categories. Possibly the slightly lower values in the poor results are significant, but the small number in that group makes the finding of doubtful value. Therefore, it appears unlikely that the poor results were on the whole attributable to low penicillin concentrations, even though in isolated instances that might have been true.

Tabulation of the cases in terms of clinical diagnosis or bacterial species or type offered little additional information and has been omitted as superfluous. Pneumonia and upper respiratory infections showed a percentage of good results of the same order as already mentioned, in spite of the fact that the latter group apparently contained more virus cases. Even in otitis media, though six out of seven patients showed good response to oral penicillin, the poor result in the seventh was difficult to explain. The otitis media in this case might have been a complication of virus infection.

TABLE IV. FREQUENCY DISTRIBUTION OF PLASMA PENICILLIN LEVELS AT THREE HOURS ON BASIS OF AGE OF PATIENTS

| | | AGE AND DOSAGE | | | | |
|---|---|---|---|---|---|---|
| | | 0-1 YR. | 1-4 YR. | 4-6 YR. | 6-10 YR. | 10 YR. AND OVER |
| WEIGHTED VALUE | PENICILLIN (U. PER C.C.) | 20,000 U Q 3 HR. | 40,000 U Q 3 HR. | 60,000 U Q 3 HR. | 80,000 U Q 3 HR. | 100,000 U Q 3 HR. |
| | 0 | | | | | |
| 1 | (0.03) | 6 | 5 | 3 | 1 | 2 |
| 2 | 0.03 | 5 | 18 | 3 | 4 | 2 |
| 3 | 0.06 | 10 | 16 | 4 | 6 | |
| 4 | 0.125 | 5 | 3 | 7 | 4 | |
| 5 | 0.25 | 9 | 2 | 1 | 1 | |
| 6 | 0.5 | 5 | 2 | | | 1 |
| 7 | 1.0 | 2 | 1 | | | |
| Total cases | | 42 | 46 | 18 | 16 | 5 |
| Modified geometric average | | 0.10 | 0.051 | 0.06 | 0.06 | 0.042 |

TABLE V. FREQUENCY DISTRIBUTION OF PLASMA PENICILLIN LEVELS AT 3 HOURS ON BASIS OF CLINICAL RESULTS

| PLASMA PENICILLIN LEVEL UNITS PER C.C. | NO. GOOD RESULTS | NO. FAIR RESULTS | NO. POOR RESULTS |
|---|---|---|---|
| 0 (<0.03) | 9 | 2 | 4 |
| 0.03 | 19 | 5 | 6 |
| 0.06 | 22 | 8 | 7 |
| 0.125 | 14 | 3 | 0 |
| 0.25 | 5 | 3 | 2 |
| 0.5 | 3 | 1 | |
| 1.0 | 2 | | |
| Total cases | 74 | 22 | 19 |
| Modified geometric average U/c.c. | 0.06 | 0.06 | 0.045 |

As pointed out in a previous study,[1, 2] failure of oral penicillin therapy may be due to one or more of four factors: (1) the presence of a causative agent that is not affected by penicillin; (2) the presence of an organism ordinarily sensitive to penicillin but which happens to be of a strain unusually resistant; (3) poor absorption of the medication; and (4) overwhelming complications. Since most of the bacterial respiratory infections have been found to respond to penicillin within forty-eight hours, it is advisable in case of unfavorable results after forty-eight hours to re-examine the situation in terms of the above four possibilities. It would probably be safer in most such cases to double the oral dosage or to resort to parenteral injections of penicillin. It has seldom been our experience in the case of respiratory infections that sulfa medication has succeeded when adequate doses of penicillin have failed. One of the important procedures in the re-examination should be the isolation of the offending organism and the determination, if possible, of its penicillin sensitivity. Even if the increased penicillin medication fails, it will at least have served to minimize complications.

There were very few instances of intolerance to the medication. The children all took the medication well. There was only occasional vomiting. There was only one case of urticaria during the period of hospital stay of these patients. It occurred on the fifth day and receded when penicillin was stopped. The almost complete innocuousness of penicillin medication as contrasted with

the relative frequency of reactions to sulfa therapy is an important consideration in the treatment of children with respiratory illness. Even if the infection turns out to have been only the common cold or an influenza attack, the oral penicillin medication will not have done any significant harm, will have been convenient, and will have prevented bacterial complications.

## SUMMARY

Oral penicillin medication with a palatable solution of soluble tablets of crystalline potassium penicillin G without buffers was used in the treatment of 168 infants and children with acute respiratory illnesses.

The dosage to be used every three hours for each age group was determined by an evaluation of assays of the plasma penicillin levels obtained after single doses in 209 hospital control infants and children. Those ranging in age from one to 12 years showed at one hour after the dose, average levels of 0.12 unit per cubic centimeter, and at three hours 0.03 to 0.05 unit per cubic centimeter. Though the dosage had been based on age, these therapeutic plasma levels were obtained with doses of approximately 3,000 units per kilogram. Infants under one year showed much higher levels. These were well sustained at three hours. Infants below three months achieved the highest levels, approximately 1.0 unit per cubic centimeter at one hour and 0.5 at three hours. These high penicillin concentrations were probably produced by the relatively poor renal function of such young infants.

In 65.7 per cent of the patients treated, good results were obtained, the fever subsiding within 48 hours with clinical improvement. Fair results were achieved in another 18.2 per cent; poor results in 16.1 per cent. Evaluation on the basis of positive bacterial cultures or high white cell counts only slightly increased the percentage of satisfactory results. Yet it was certain that a virus component was present in many cases. The plasma penicillin levels obtained were of the same order as those found in the assays. Urticaria occurred in only 1 case.

Oral administration of penicillin without buffers was seen to be a convenient and satisfactory method of treatment of respiratory infections in children, if adequate dosage was used and if failure of response in 48 hours was made the signal for increased dosage or change to parenteral penicillin.

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# GLOMERULAR FILTRATION RATE, EFFECTIVE RENAL BLOOD FLOW, AND MAXIMAL TUBULAR EXCRETORY CAPACITY IN INFANCY

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THIS paper reports studies on the development of glomerular and tubular function in children from early postnatal life to the age of 2 years, with special reference to the correlation between renal function and body surface area.

## METHODS

Twenty-three series of clearance measurements, ten by the single period method and thirteen by the multiple period method, have been made on infants who showed no evidence of renal or cardiovascular disease.* The rate of glomerular filtration (mannitol clearance, $C_M$), the effective renal plasma flow (p-aminohippurate clearance, $C_{PAH}$) and maximal tubular excretory capacity for p-aminohippurate ($Tm_{PAH}$) were determined by methods essentially as described by Goldring and Chasis[4] for adults. Mannitol and PAH were administered by intravenous infusion into a scalp vein of the very young infants, or into an ankle, hand, or antecubital vein in older infants, at rates estimated, on the basis of body weight and the expected renal clearances, to give suitable plasma concentrations. In general, the sustaining infusion of PAH and mannitol consisted of 250 c.c. of normal saline administered at a rate of 2 to 4 c.c. per minute. The priming doses of PAH and mannitol were injected into the infusion tubing. An equilibration period of thirty minutes followed the start of the sustaining infusion. For $Tm_{PAH}$ a second priming dose was injected into the infusion tubing and the requisite PAH was added to the residual (ca. 150 c.c.) infusion fluid. Urine collection was resumed after a second thirty-minute equilibration period. Blood specimens were taken from the antecubital vein, the femoral vein, or the femoral artery. The bladder was catheterized with No. 8 to No. 12 French catheters and washed out at the end of each discard or urine collection period with sterile saline. Mannitol was determined in later tests by the chromotropic acid method of Corcoran and Page (personal communication).

## RESULTS AND DISCUSSION

In the infants studied here, the filtration rate increases from about 3 c.c. per minute in the first week of life to 40 to 50 c.c. per minute at the end of the first year (Fig. 1). Considered in relation to age alone, one cannot say from the present data when the stable adult value of 124 c.c.[4] would be reached. How-

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*These infants were patients on the Pediatrics Service (New York University College of Medicine) of Bellevue Hospital. We are indebted to Dr. Emmett Holt for his cooperation in these studies.

ever, McIntosh and associates[9] have shown that, when corrected to standard body surface area (1.73 square meters) the urea clearance has apparently the same value in children from 2 years of age and upward as it has in adults, implying that variations in this aspect of renal function as related to body size are roughly correlated with body surface area. Schoenthal and associates[12] subsequently showed in nine normal infants ranging in age from 2 to 11 months, that the urea clearance corrected for surface area agreed with the values observed by Van Slyke and his co-workers and with those reported in terms of the Addis ratio[1] for older children and adults. Stewart[16] and Taylor and associates[17] showed in the dog and rabbit, respectively, that renal weight was more closely related to body surface area than to body weight, and Addis and his co-workers corrected the urea excretion ratio in man for surface area. The fact that the coefficient of variation of the data so calculated has the small magnitude of 13.1 per cent indicates a high degree of correlation. The reality of this correlation has subsequently been widely accepted in respect to renal function as related to body size among adults, as well as among individuals of various ages.

We have examined our data to determine if the correlation between renal function and body surface area extends back to ages under 2 years. It appears that such is the case: considered as an order of magnitude only, the adult mean value for the filtration rate of 124 c.c. per minute per 1.73 square meters appears to be reached in some infants as early as 10 to 20 weeks, as will be seen in Fig. 2.

Young and McCance[18] measured the urea and inulin clearances in infants in the first year of life, and concluded that in general the filtration rate, when corrected to standard surface area, was lower than the normal adult value. However, they used the single injection method with rapidly falling blood curve, a technique which may yield lower clearance values than our method, which involves the infusion of 200 to 300 c.c. of saline. We find subnormal mannitol clearances only in the first month or so, but in this period our results confirm those of Young and McCance.

The renal plasma flow (Fig. 1) increases from about 12 c.c. per minute in the first week to about 140 c.c. per minute at the end of the first year. Again, the data so presented do not reveal when the adult stable value would be reached. However, when compared on the basis of body surface area (Fig. 2), the adult mean value of 646 c.c. per minute per 1.73 square meters[4] (average of male and female subjects) appears to be reached in some cases as early as the thirtieth week.

$Tm_{PAH}$ increases from 2.6 mg. per minute in the first week to 25 mg. per minute at one year (Fig. 1). When corrected for body surface area (Fig. 2), $Tm_{PAH}$ reaches the normal adult value of 77.5 mg. per minute[3] per 1.73 square meters at about thirty weeks.

It appears from the above relationships that the magnitudes of the filtration rate, renal blood flow, and tubular excretory mass are adjusted at an early age (under one year) to the metabolic requirements of the body, using the surface area as an approximate correlated index to general metabolism. However,

in the early stages of infancy, when this adjustment has not yet been perfected, the three functions develop at different rates, as judged by this standard of reference. The relative rates of increase of these three variables are best revealed by examination of the simultaneous ratios.

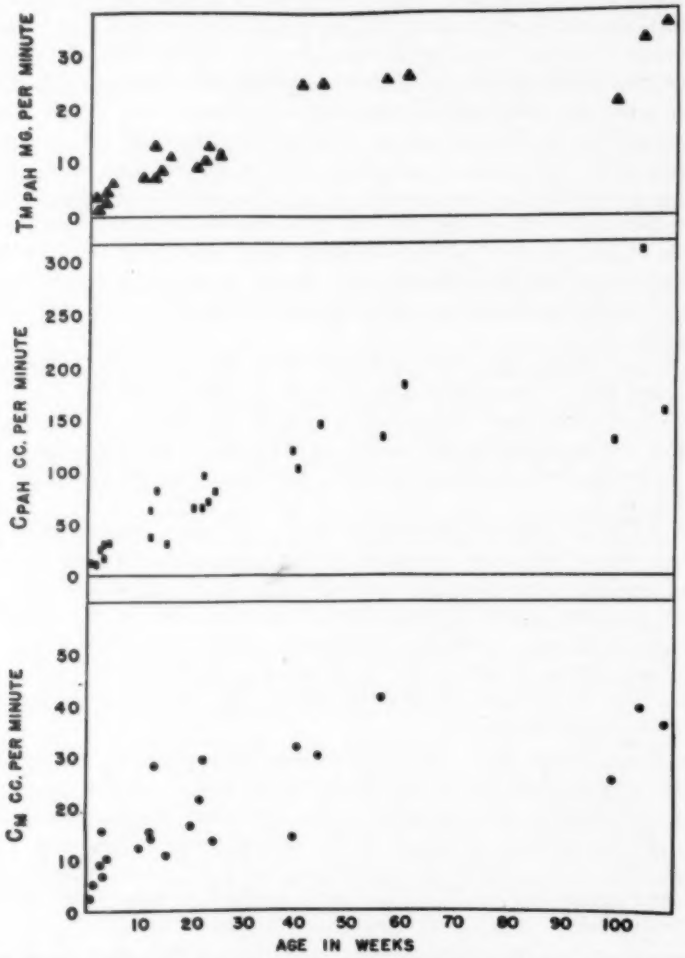


Fig. 1.—Maximal tubular excretory mass (top), effective renal plasma flow (middle) and filtration rate (bottom) in infants in relation to age in weeks.

The $C_{PAH}/Tm_{PAH}$ ratio (Fig. 3), high in two of the youngest infants, has close to the adult value of 7.74[3] in all others, suggesting that a proportional increase in renal blood flow accompanies the development of the renal tubules.

The $C_M/Tm_{PAH}$ ratio is higher than the adult value of 1.53 in the three youngest infants but decreases to the latter before the end of the first year.

The initially high value could be explained by anatomic imbalance between glomerular and tubular development, the former being favored by disproportionate large glomerular surface or increased glomerular pressure.

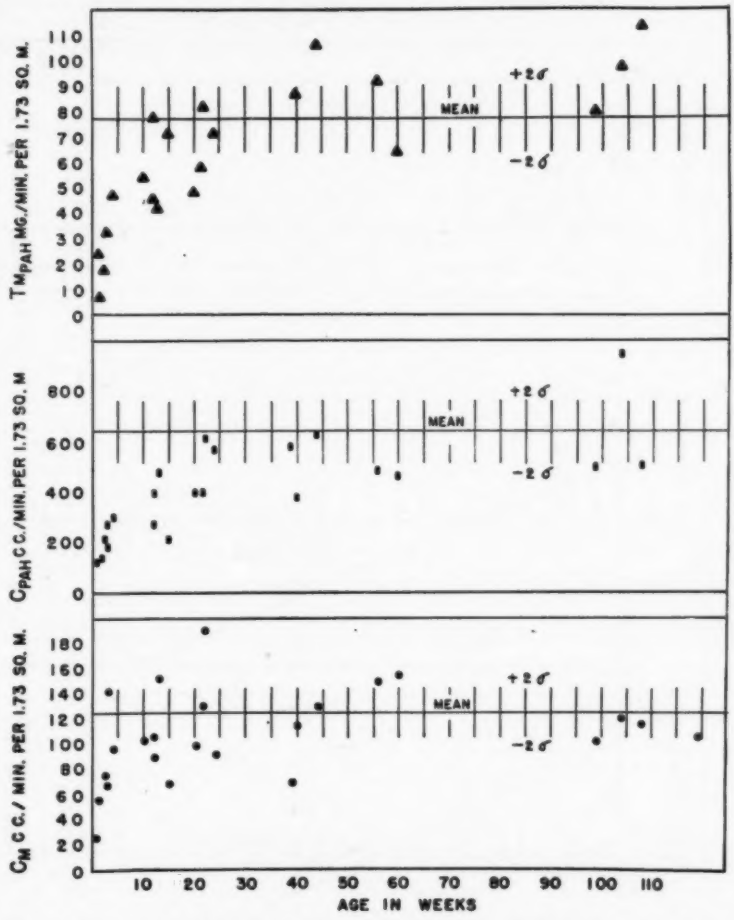


Fig. 2.—The data shown in Fig. 1 corrected to 1.73 square meters of body surface area. The horizontal line represents the mean standard adult value plus or minus 2σ.

The filtration fraction ($C_M/C_{PAH}$) is definitely above the adult value (0.16) during the first few months, falling toward but scarcely reaching the latter at one year, a circumstance which could be explained by imbalance between glomerular and tubular development, as suggested above, or by a low extraction ratio in the blood perfusing the tubules. The extraction ratio* of PAH is not known in the infant kidney, and the possibility of a low value cannot be dis-

*The most recent figures indicate an average of 92.5 per cent in the adult human kidney.[3]

missed. However, the fact that the $C_{PAH}/Tm_{PAH}$ ratio is identical with the adult value shows that each functional unit of excretory tissue has available to it at least as much blood as in the adults; if the extraction ratio across this excretory tissue is subnormal, then this tissue must have an excessive supply of

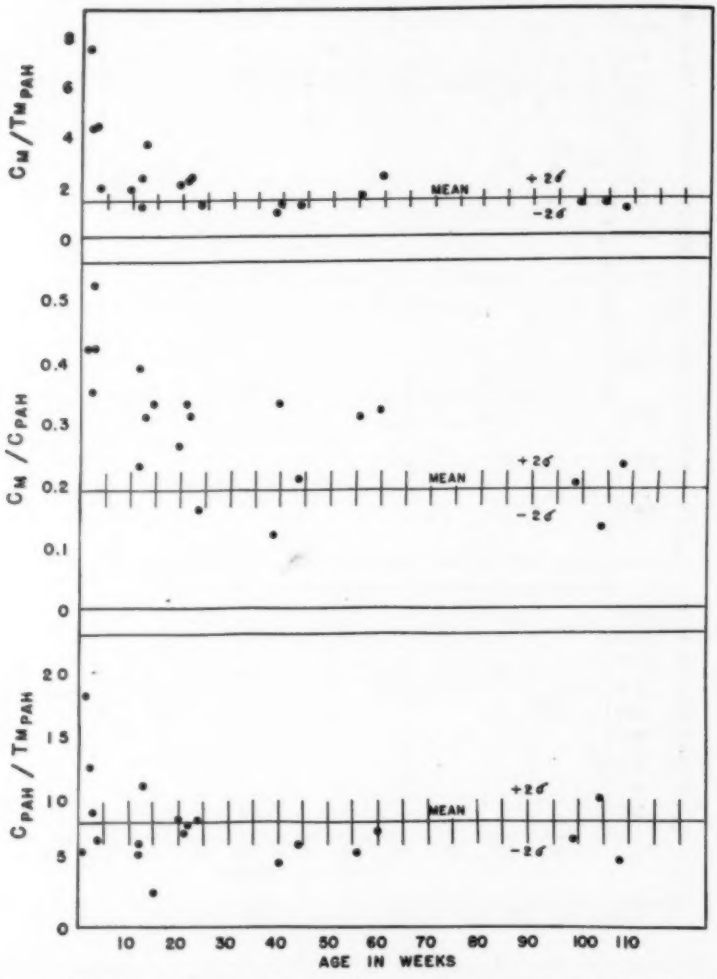


Fig. 3.—Filtration rate per unit of tubular excretory mass (top), filtration fraction (middle) and effective renal plasma flow per unit of tubular excretory mass (bottom) in infancy, the horizontal lines representing the mean standard adult value plus a minus $2\sigma$ should be drawn at 0.16 instead of 0.20.

blood, and the constancy of the ratio $C_{PAH}/Tm_{PAH}$ from birth onward would require that the blood flow decrease *pari passu* as the extraction ratio rises to the normal. Alternatively, an excess of filtrate over effective renal plasma flow

might be attributable to the presence of postglomerular vascular channels, the blood of which is not available to the tubules for PAH extraction. Neither explanation can be excluded in the absence of measurements of the extraction ratio, but until the extraction ratio is known a normal value will be assumed, and the excessive $C_M/Tm_{PAH}$ ratio will be interpreted as indicating simple dynamic glomerular-tubular imbalance.

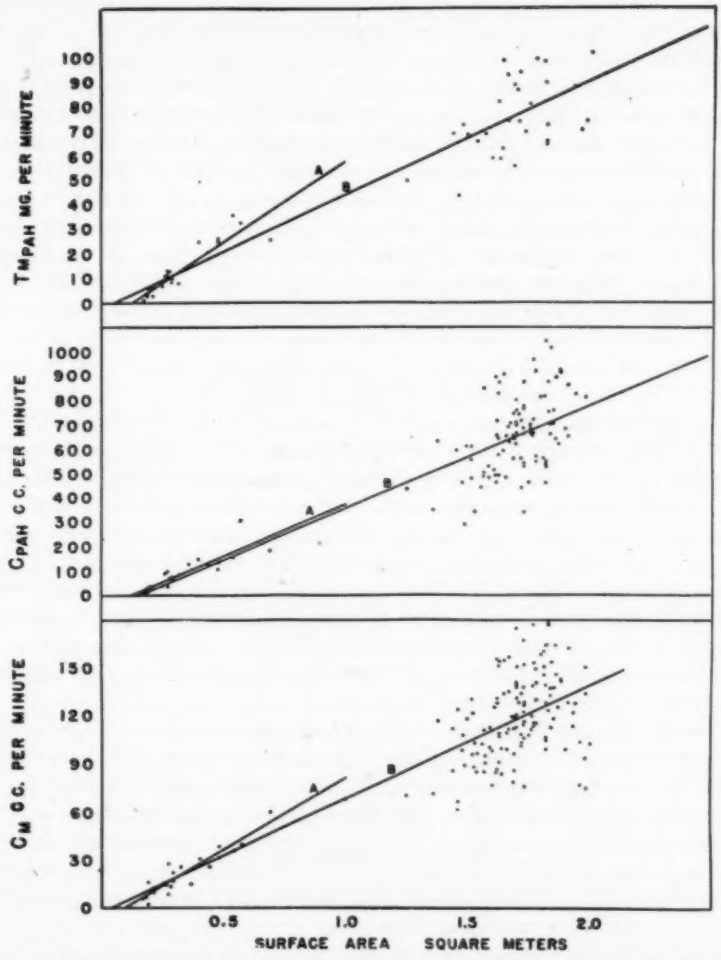


Fig. 4.—Absolute values of tubular excretory mass (top), effective renal plasma flow (middle) and filtration rate (bottom) in relation to body surface area in infants and adults. The regression lines are discussed in the text.

It is known that in early infancy the loop of Henle is short and increases with advancing age,[10] but this observation throws no light on the relative functional development of glomeruli and tubules, particularly since the length of

the loop of Henle is highly variable in the adult kidney. But since the number of nephrons does not increase after birth, despite a large increase in renal weight, it is clear that there is a considerable postnatal increment of tubular tissue in each nephron. It is possible that in the infant's kidney glomerular function early reaches a relatively normal value (i.e., as related to body surface area) not only because it has its full complement of glomeruli at birth, but because of a relatively large glomerular surface area possibly supplemented by relatively high glomerular pressure. Stated in another way, the requirement that physical space must be left for tubular development as a concomitant of growth is responsible for the fact that the newborn infant has a greater deficiency of tubular than of glomerular tissue, a differential which is corrected in the first year of life. Such an anatomic imbalance between glomerular and tubular development would explain (a) the rapid increase of the filtration rate to the adult requirement, relative to body surface area; (b) the slower development of tubular excretory tissue and (c) of effective renal blood flow; and as corollary of these conditions, (d) the relatively high value of $C_M/Tm_{PAH}$ in early infancy. The fact that the value of $C_{PAH}/Tm_{PAH}$ attains its adult value shortly after birth indicates that the vascularization of the kidney proceeds parallel with the development of tubular tissue.

In this interpretation it must be noted that the expansion of glomerular surface per se would not lead to an increase in the filtration rate or filtration fraction, so long as filtration equilibrium is reached in the glomeruli, unless the glomerular pressure were likewise increased.[5, 14] However, if filtration equilibrium is not reached in the glomeruli, but rather in the postglomerular vessels, the time of exposure of blood in the glomeruli is important in determining the filtration rate, and expansion of the glomerular surface, either by prolonging the time or effective area of exposure, would permit equilibrium to be approached more closely, and both the filtration rate and filtration fraction would be increased in consequence of this fact. The available data on glomerular dynamics do not permit us to answer this question, and the explanation of a high filtration fraction must be left equivocably assigned to either increased glomerular surface or glomerular pressure.*

It must also be noted that the terms "tubular development" indicate only one aspect of tubular function, namely, the maximal capacity to excrete PAH. It is conceivable that other aspects of tubular function may not show the same relationship as is reported here. McCance and Young[8] and Heller[7] have shown that the kidney up to 14 days of age cannot excrete a concentrated urine, and Heller has shown that the kidney at 6 days is insensitive to the antidiuretic hormone, indicating that the capacity for osmotic work is more slowly developed than any of the above functions.

Gruenwald and Popper[6] have called attention to the circumstance that up to birth the glomeruli are covered with cuboidal or high columnar epithelium which tends to compress the glomerular capillaries. After birth these loops expand and the blood content apparently increases. Persistence of this em-

*If the extraction ratio in blood perfusing cells measured in $Tm_{PAH}$ is low in the infant kidney (*vide supra*), the filtration fraction will be correspondingly increased, and in such a case filtration equilibrium may be assumed to be reached in the glomeruli.

bryonic epithelial investment in early postnatal life would tend to reduce the filtration rate. If so, the relatively larger size of the glomeruli or increased glomerular pressure must more than compensate for this deficiency, since by two standards of reference (filtration rate per unit of surface area and the filtration fraction) the filtration rate at birth is supernormal.

Accepting the principle that (relative to aging) renal function can best be correlated with body surface area, it is of interest to compare the rate of development up to 2 years with the entire span from birth to adulthood. In Fig. 4 we have shown the data on infants with those on adults[3, 13, 15] and calculated the regression lines for (A) infants alone and (B) infants plus adults. Only in the case of $C_{PAH}$ are these two regression lines practically identical; here there is only 0.18 chance in 100 that the two lines represent different populations, indicating that development in infants does not depart from development over the entire life span. In the case of $C_M$ and $Tm_{PAH}$, the regression lines A and B deviate so markedly as to suggest that one regression line representative of the entire life span would be concave to the horizontal axis. The positive intercept of regression line A on the horizontal axis (nominally indicative of zero function at an average surface area of 0.11 square meter) is physiologically uninterpretable at the present time.

## SUMMARY

1. Glomerular filtration, effective renal plasma flow, and maximal tubular excretory capacity have been measured in twenty-one normal infants ranging in age from one-half to 110 weeks.

2. When corrected for surface area, the adult mean value for the filtration rate is reached in some infants in ten to twenty weeks, for effective renal plasma flow and maximal tubular excretory capacity in thirty weeks.

3. If the body surface area is used as an index to general metabolism, the filtration rate, renal blood flow, and tubular excretory mass are adjusted before the end of the first year to the metabolic requirements of the body. However, in the first two or three months of life the three functions develop at different rates. The fact that the normal adult value of the $C_{PAH}/Tm_{PAH}$ ratio is observed in nearly every infant suggests that the renal blood flow increases in proportion to the development of the renal tubules. The $C_M/TM_{PAH}$ and $C_M/C_{PAH}$ ratios in early infancy are, however, higher than the adult values, indicating functional imbalance between glomeruli and tubules in favor of the former. This imbalance might be related to increased glomerular pressure, disproportionally large glomerular surface, or decreased PAH extraction ratio; it is suggested that large glomerular surface and increased pressure are, perhaps, responsible for glomerular hyperfunction.

## ADDENDUM

Since this study was completed, Corcoran and Page (J. Biol. Chem. 170: 165, 1947) have reported that, using their chromotropic acid method, the mannitol inulin clearance ratio averages 0.902. This has been confirmed in this laboratory. No correction has, however, been applied to our data, since we believe it better to present the uncorrected data at this time.

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# A NEW ANOMALY OF THE AORTA

## Left Aortic Arch With Right Descending Aorta

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A NUMBER of abnormalities of the aorta, either in its course or in the origin of its brachiocephalic vessels, have been described. Most of them can now be detected by means of x-ray. The more common anomalies of the aorta will be reviewed, and another added, a left aortic arch with a right descending aorta. A review of the literature has failed to reveal any record of such an anomaly.

No accepted method of classifying the various aortic arch anomalies exists; consequently, the following table is presented merely as a working basis for this discussion.

A. Right aortic arch
   1. Right aortic arch with right descending aorta
   2. Right aortic arch with retroesophageal aorta
      a. Left descending aorta
      b. Right descending aorta (aortic diverticulum)

B. Double aortic arch
   1. Right arch serving as main channel
   2. Left arch serving as main channel

C. Anomalous subclavian artery
   1. Arising from aortic arch or descending aorta
   2. Arising from a right or left aortic arch

D. Coaretation of the aorta

E. Complete interruption of the isthmus of the aorta

F. *Left aortic arch with right descending aorta*

### RIGHT AORTIC ARCH

The right aortic arch is a well-known anomaly but much confusion arises in the literature in that there are two main types: in one, the aorta courses behind the esophagus, and in the other it does not, yet both of these conditions are usually described under the same name. Frequently one finds the title "right aortic arch" although the description which follows may be of either type. In order to eliminate any misunderstanding as to the type referred to, we shall differentiate them by the more descriptive terms of right aortic arch with right descending aorta and right aortic arch with retroesophageal aorta.

The right aortic arches are not to be confused with dextroposition of the aorta, which means that the aortic orifice overrides the right ventricle, nor with transposition, in which condition the aorta is given off entirely from the right ventricle.

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### RIGHT AORTIC ARCH WITH RIGHT DESCENDING AORTA

Embryologically this type of anomaly results from the persistence of the fourth right arch, instead of the fourth left, and represents the normal aortic arch as seen in birds. Although it had been reported many times in man after observation at autopsy, it was not until 1924 that Assmann[3] showed it could be diagnosed roentgenographically during life.

The abnormality might best be visualized as a mirror image of the normal left aortic arch, although anatomically this is inexact (except in cases of situs inversus). The aorta arises from the left ventricle and begins its upward course toward the right as does the normal left aortic arch. Instead of arching to the left, however, it continues to the right of the esophagus and trachea, then arches over the right main bronchus and descends on the right side. It maintains this course to the right of the esophagus but usually crosses back to the left side in the lower portion of the thorax and passes through the diaphragm in the normal position.[5]

Assmann suggested that all cases of right aortic arch (with right descending aorta) were associated with congenital defects in the heart since this was the situation in his cases. This may not be invariable, but in our experience it is quite common in the cardiac malformations which lead to cyanosis. In a group of over 500 cyanotic children seen in this clinic, 20 to 25 per cent of them have had a right aortic arch with right descending aorta.[19]

### RIGHT AORTIC ARCH WITH RETROESOPHAGEAL AORTA

In this anomaly the aorta is identical with that in the preceding abnormality as far as the level of the arch but from there on it is grossly different. After ascending to the right of the esophagus and trachea the aorta turns sharply to the left and courses behind the esophagus, displacing it anteriorly. It then emerges on the left of the esophagus and trachea from whence it turns caudally and descends on the left of the spine, though somewhat more to the right than does the normal descending aorta.[11]

In some cases the aorta may not cross completely to the left behind the esophagus. In these, the aorta, after crossing retroesophageally, turns sharply back to the right and caudally to descend on the right. The retroesophageal portion is in the form of a diverticulum which usually gives rise to the left subclavian artery and sometimes to the ductus arteriosus.[5, 15]

Although the right aortic arch with retroesophageal aorta is the type of anomaly which has been associated frequently with "dysphagia lusoria," the use of the term in this condition is somewhat erroneous. It was used originally by Bayford[4] to describe the dysphagia due to an anomalous subclavian artery. A few patients do present symptoms of dysphagia or dyspnea, but the great majority are asymptomatic and the condition is either noted incidentally at autopsy or during routine fluoroscopy. Furthermore, in the symptomatic cases, there seems to be no relationship between the degree of displacement of the esophagus and the production or severity of symptoms.[7]

In contrast to the right aortic arch with right descending aorta, the great majority of these defects seem to occur with an otherwise normal heart.

Arkin[1] is given credit for having been the first to demonstrate that this type of abnormality could be distinguished during life by means of x-ray. The radiographic findings are quite characteristic, particularly with regard to the changes produced by the retroesophageal aorta, but difficulty may arise in differentiating this condition from a double aortic arch. This difficulty is understandable since this type of right aortic arch is an integral part of the double aortic arch. However, inasmuch as they are each distinct anomalies, an attempt at exact diagnosis should be made.

In the literature this type of right aortic arch appears to be by far the more common. This may be only an apparent preponderance since the right aortic arch with right descending aorta can more readily escape recognition. The oblique views in that variety are not striking and may be passed as normal but in the right aortic arch with retroesophageal aorta the oblique views are so characteristic and so different from the normal that they can hardly be ignored.

### DOUBLE AORTIC ARCH

The characteristic findings in a double aortic arch, or aortic ring, were also initially described by Arkin[2] from x-ray observations. The diagnosis of this anomaly is of more than academic interest since Gross[10] has described a method for surgical correction of the defect in cases in which the "ring" produces symptoms.

In this anomaly there is a persistence of both the right and left aortic arch, resembling closely the type of aorta seen normally in reptiles. The right arch is usually of normal size and serves as the main systemic channel, whereas the left usually persists as a partially or completely obliterated tube. The reverse may also be true although it is less common. Sprong and Cutler[16] in their review, cite fifteen cases of double aortic arch, only two of which presented the left arch as the larger vessel. More recently, another case of this type has been reported, the condition having been proved at the time of operation.[18]

The right arch courses behind the esophagus in much the same fashion as does the previously described right aortic arch with retroesophageal aorta. The smaller left arch is usually given off the ascending portion of the right arch and follows the course of a normal left aortic arch anterior to the trachea. It then joins the descending portion of the right arch posteriorly and to the left of the esophagus. It can readily be seen how this arrangement might lead to symptoms of obstruction of the esophagus and trachea.

As mentioned before, the x-ray picture in this anomaly is quite similar to that of a right aortic arch with retroesophageal aorta and the differentiation of the two may be quite difficult. In some cases it is possible to visualize in the oblique views the left aortic arch coursing anterior to the trachea. This, in addition to the demonstration of the retroesophageal aorta by the administration of barium, establishes the diagnosis.

Neuhauser[13] presents cases in which there is a bilateral indentation of the esophagus in the anterior-posterior view resulting from pressure on both sides of the esophagus by the right and left aortic arches. Additional information

is obtained by the demonstration of tracheal deformity after the installation of lipiodal or other suitable radio-opaque oils.

This condition may or may not lead to symptoms of esophageal or tracheal obstruction, depending on the degree of constriction by the resultant vascular ring. Certainly in infants it is of serious moment as is well shown in Wolman's report.[20]

### ANOMALOUS SUBCLAVIAN ARTERY

Variations in the origin of the brachiocephalic vessels from the aorta are many. For the most part, they are of little clinical significance and, except for cases in which there is an anomalous retroesophageal subclavian artery, they cannot be diagnosed without resorting to special radio-opaque substances and elaborate x-ray techniques.

Although in the right aortic arches the innominate artery gives rise to the *left* subclavian and carotid arteries instead of the *right* subclavian and carotid, this is not to be considered as a separate anomaly. In fact, under such circumstances it is quite usual since the innominate artery is normally the first vessel to be given off the aorta and courses to the side opposite the arch.

The most common type of abnormality in this category, and one that can be detected by x-ray, is the anomalous subclavian artery which arises from the descending aorta or as the last branch from the aortic arch. This anomalous vessel may pass in front of the trachea, between it and the esophagus, or behind the esophagus.[12] The retroesophageal course is by far the most common and in this situation it displaces the esophagus anteriorly much the same as does the aorta in a right aortic arch with a retroesophageal aorta. However, the displacement of the esophagus by the subclavian artery is never so marked as by the aorta and it is usually situated at a different level than the aortic arch.

A retroesophageal right subclavian artery must of necessity arise from either a left aortic arch or a left descending aorta,[9, 14] whereas an anomalous left subclavian artery must be given off from a right aortic arch or right descending aorta.[8]

### OTHER ANOMALIES OF THE AORTA

Coaretation of the aorta and complete interruption of the isthmus of the aorta (absence of the aortic arch) are also to be listed under abnormalities of the aorta. However, a discussion of these two anomalies will not be included in this report since we are more concerned with variations in the *course* of the aorta.

### LEFT AORTIC ARCH WITH RIGHT DESCENDING AORTA

This appears to be an entirely new anomaly. So far as is known, it has never been described. The following report of two cases establishes its existence and demonstrates the fairly characteristic x-ray picture which it produces.

Both patients were originally considered to have a tetralogy of Fallot and consequently were deemed candidates for the Blalock-Taussig operation.[6a] The abnormal course of the aorta was determined by fluoroscopy and x-ray after the administration of barium mixture and the anomaly was demonstrated at the time of operation.

## CASE REPORTS

CASE 1.—M. P., a 7-year-old white female, had a history of cyanosis first manifest at 10 days of age. With the onset of activity dyspnea became evident and because of it the patient was markedly incapacitated. She was able to walk only about one-half block at the time she was seen in the clinic. When tired, she would squat to rest.

Physical examination revealed a very cyanotic and plethoric young girl with no dyspnea while at rest. She showed rather marked clubbing of the fingers and toes. By percussion, the heart was found to be approximately normal in size. A definite precordial thrill was palpable and a harsh systolic murmur was heard over the entire precordium, loudest along the left sternal border.

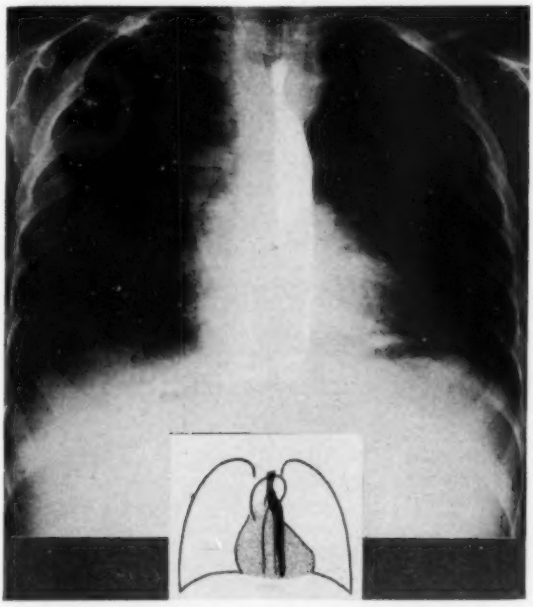

Fig. 1.—M. P. The barium descends far to the left of the midline and there is no shadow of aorta between aortic knob and upper left border of the heart.

Fluoroscopically the heart was small. In the anterior-posterior and right anterior oblique views there was an absence of fullness of the pulmonary conus. In the left anterior oblique view the pulmonary window was found to be quite clear. There were minimal vascular markings in the hili of the lungs with no evidence of pulsations in these vessels. These findings were considered consistent with a diagnosis of tetralogy of Fallot.

The visualization of the esophagus by the routine administration of a barium mixture is illustrated in Figs. 1, 2, and 3. In the anterior-posterior view (Fig. 1) the barium-filled esophagus is seen to be indented on its left margin by the arch of the aorta. This is the usual finding in the normal, left aortic arch and establishes the presence of a left-sided arch in this patient. There are two unusual features, both of which help to direct attention to this distinctive anomaly. One is the absence of any vascular or cardiac shadow to the left of the barium column for a short distance between the aortic knob and the upper left border of the heart. The other is the manner in which the esophagus descends, far to the left of the midline. These two findings suggest that the esophagus, below the level of the arch, courses to the left of the descending aorta instead of in its normal position to the right of the thoracic aorta.

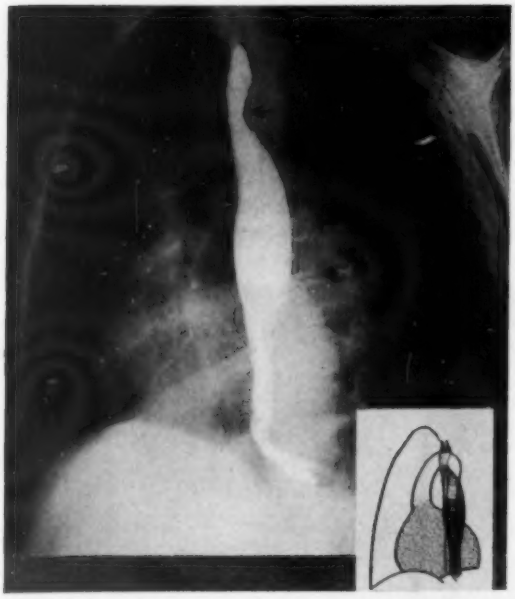

Fig. 2.—M. P. Left anterior oblique view shows anterior displacement of barium-filled esophagus (arrow) at the level of the aortic arch, caused by retroesophageal aorta.

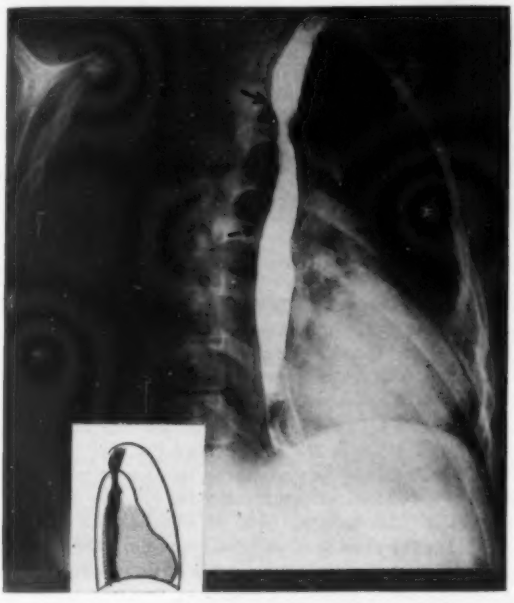

Fig. 3.—M. P. Right anterior oblique view. The anterior displacement of the esophagus (between arrows) is over a wider area than in Fig. 2. This is due to retroesophageal aorta emerging diagonally on the right.

Although the actual course of the descending aorta is not demonstrated in the x-ray, the anterior displacement of the barium-filled esophagus in the oblique views (Figs. 2 and 3) is reliable evidence that it crosses retroesophageally. This anterior displacement has been described previously in right aortic arch with retroesophageal aorta and in double aortic arch; it is produced by the aorta as it passes between the esophagus and the anterior surface of the spine. Since it has been demonstrated in the anterior-posterior view that the aorta arches to the left, it can be seen readily that the aorta must course from left to right behind the esophagus. That it then descends on the right is again substantiated by the absence of vascular shadow to the left of the esophagus between the aortic knob and left cardiac border and by the extreme left-sided descent of the esophagus as seen in Fig. 1. These findings show that the aorta, descending on the right, pushes the esophagus to the left.

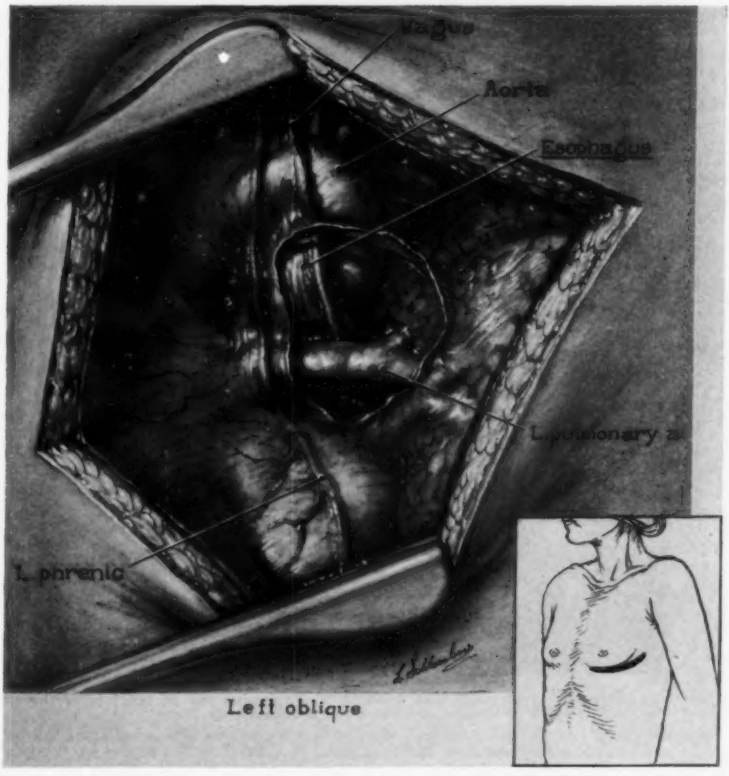


Fig. 4.—M. P. The aorta is shown crossing behind the esophagus, the latter being pushed to the left. Note the wide separation between aortic arch and left pulmonary artery.

The more marked anterior displacement of the barium column in the left anterior oblique view (Fig. 2) as compared to that in the right anterior oblique view (Fig. 3) can be explained on the basis of a transverse position of the aorta as it begins its retroesophageal course on the left and a somewhat diagonal position as it emerges to descend on the right (see inset figures).

By reconstruction of the various impressions that the aorta made upon the esophagus, it can be deduced that the aorta courses normally to the left as far as the arch, then passes

behind the esophagus where it turns caudally, emerges on the right, and maintains its right-sided descent through the thorax.

Preoperative diagnosis was a tetralogy of Fallot and a left aortic arch with right descending aorta. The patient was admitted to the hospital for surgery and she was operated on Oct. 24, 1946, by Dr. Alfred Blalock.

The chest was opened on the left in the third interspace. The pulmonary artery was visualized and found to be a fair-sized vessel with strong pulsation. The pulmonary pressure measured 470 mm. of water. Since a pulmonary pressure of more than 360 mm. of water is considered a contraindication, no anastomosis was done.

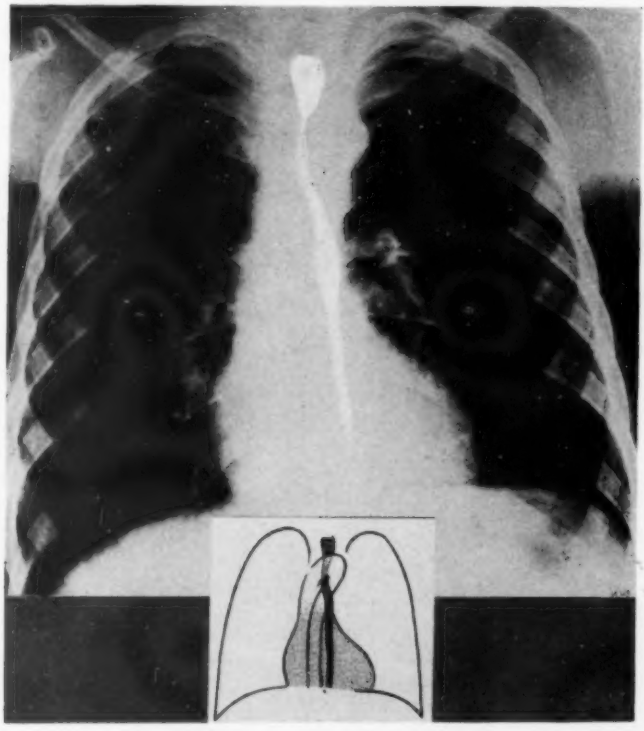

Fig. 5.—C. P. The left aortic arch and descent of esophagus far to the left of the midline is shown (barium column retouched).

The mediastinal structures were then explored to determine the course of the aorta. The aortic arch was found to be on the left at a slightly higher level than normal and there was an unusually wide separation between the arch and the left pulmonary artery. This is shown in Fig. 4. The brachiocephalic vessels were given off in the normal order. After the left carotid was given off, the aorta turned caudally and toward the right, passing behind the esophagus. The esophagus was seen to course to the left of the vertebral column and by palpation the aorta was found to descend on the right of the esophagus.

The chest was closed and the patient was returned to the ward. She made an uneventful recovery but, of course, was not helped by the operation.

CASE 2.—C. P., an 11½-year-old white male, was referred from Hackensack Hospital, New Jersey. A diagnosis of congenital heart disease was first made when the patient was one

year old. Between the age of one and 2 years, cyanosis became evident. At about 2 years of age clubbing became noticeable. He was seen on numerous occasions at the Hackensack Hospital from 2 to 11 years of age, and over this period of time there had been a gradual rise in his red blood cell count from 4.1 to 8.6 million. At eleven years, because of his marked physical incapacity and his poor home conditions, he remained in the hospital as a boarder.

Physical examination at the Johns Hopkins Hospital revealed a thin white male of Italian extraction. He was moderately cyanotic and plethoric and showed marked clubbing of the fingers and toes.

Examination of the heart revealed a loud, blowing, systolic murmur over the sternum, loudest in the third right interspace. It was rough in quality along the left sternal border.

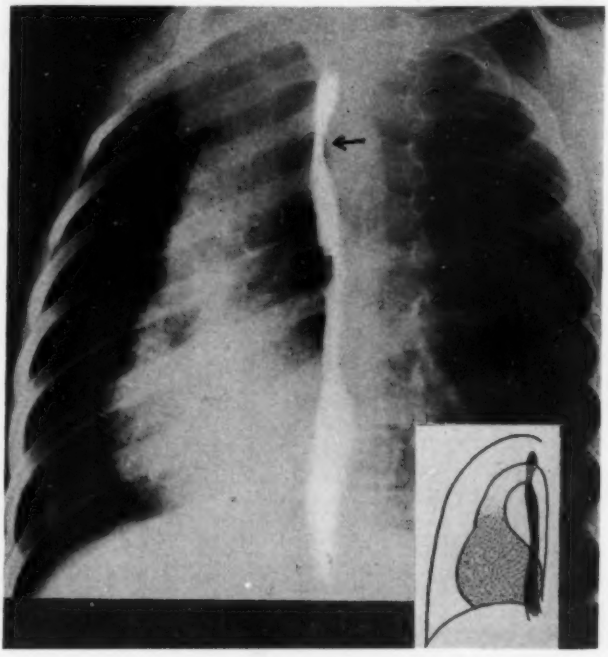

Fig. 6.—C. P. Left anterior oblique view, showing the anterior displacement of the esophagus (arrow) caused by the retroesophageal aorta.

By fluoroscopy the heart was found to be small. In the anterior-posterior view there was a marked concavity in the region of the pulmonary conus and in the right anterior oblique the absence of conus was again evident. In the left anterior oblique the pulmonary window was clear. There were minimal vascular markings in the hili of the lungs and no pulsation of these vessels was evident. Routine barium swallow gave evidence of a left aortic arch but the abnormal course of the esophagus, evident in the oblique views, was not appreciated at the time.

The patient's cardiac condition was diagnosed as a tetralogy of Fallot and he was considered as a candidate for operation. He was sent back to the Hackensack Hospital to await an opening in the operative schedule.

Upon his return to our hospital for operation, his x-rays were reviewed and the great similarity to those of the first patient was noted. This additional anomaly was therefore added to the diagnosis.

In the anterior-posterior view (Fig. 5) the presence of a left aortic arch is quite evident. The barium-filled esophagus is seen to course in the same characteristic fashion as in Case 1 (see Fig. 1). There is no vascular nor cardiac shadow to the left of the barium column between the aortic knob and the upper left border of the heart. Below this the esophagus is seen to descend far to the left of the midline.

In the left anterior oblique view (Fig. 6) the esophagus is displaced anteriorly at the level of the arch and is comparable to the same view in the first case (see Fig. 2). This is again the result of the aorta crossing retroesophageally. Since the arch lies on the left there is little question that the aorta must course from left to right behind the esophagus.

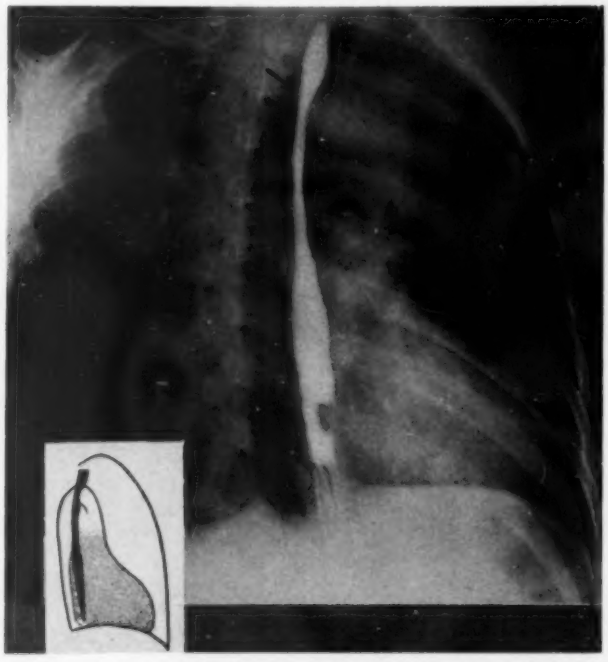

Fig. 7.—C. P. Right anterior oblique view shows slight anterior displacement of the esophagus (between arrows) over a wide area.

The right anterior oblique view (Fig. 7) in this case does not show as much anterior displacement of the esophagus as in Case 1 (Fig. 3). This is explained on the basis of the aorta emerging on the right of the esophagus in a more vertical fashion than in the previous case and consequently exerting its effect on the esophagus to a lesser degree and over a greater distance.

The patient was operated on Jan. 31, 1947, by Dr. William Longmire. The chest was opened on the right in the third interspace. The pulmonary artery was found to be small and it was apparent that the pulmonary pressure was low. Consequently, no direct measurement of the pulmonary pressure was made.

The right subclavian artery was isolated and found to arise from the innominate artery. An anastomosis was then performed between the end of the right subclavian and the side of the right pulmonary artery according to the usual technique. (For details of the surgical procedure the reader is referred to the work of Dr. Alfred Blalock.[6a, b, c, d])

The exposure was poor for demonstrating the course of the aorta. The absence of the aortic arch on the right gave indirect proof that it was a left aortic arch. The descending

aorta was found by palpation to lie somewhat to the left of the midline. However, the esophagus was not visualized to the right of the descending aorta and consequently was assumed to be on the left of it. The proof in this case was almost entirely by inference.


## SUMMARY

The more common anomalies of the aorta and origin of the brachiocephalic vessels are reviewed.

Two cases of the hitherto undescribed anomaly of left aortic arch with right descending aorta are presented and illustrated by characteristic x-ray findings. The anomaly in each case was diagnosed preoperatively during fluoroscopic and x-ray examinations, and was proved at the time of operation.


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# THE TREATMENT OF PERTUSSIS AND PNEUMONIA COMPLICATING PERTUSSIS

## The Role of Hyperimmune Gamma Globulin* and Sulfadiazine

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PERTUSSIS, and, more particularly, pneumonia complicating pertussis, remain a prominent cause of death in infants. Fox and Knott[1] found the mortality rate of 362 hospitalized patients with pertussis to be 8.6 per cent. Seventy per cent of the total number of deaths in their series occurred in the group less than one year old. In this youngest age bracket the case fatality rate was 20 per cent. Similarly, Davis and Carroll[2] found that 60 per cent of all deaths from whooping cough occurred during the first year of life.

During the past several years, two groups of agents have appeared which have given promise of favorably affecting the morbidity and mortality of pertussis.

Bradford[3] in 1935 reviewed the literature concerning the use of whole blood and convalescent serum and found that these agents were of value in passive prophylaxis of the disease but were worthless in treatment. His results were confirmed by Meader,[4] and Cohen and associates.[5] Likewise, Cohen and Lapin[6] found adult serum to be effective in passive prophylaxis. The more recently developed[7, 8] hyperimmune serum has been demonstrated to be of striking value in the prevention of pertussis in exposed susceptibles by several investigators.[6, 7, 9] Especially encouraging have been reports concerning the use of hyperimmune serum in the active treatment of pertussis.[5, 7, 9, 10] McGuiness and his co-workers[9] obtained excellent results in 38.5 per cent of patients, good results in 31.7 per cent and moderate results in 19.9 per cent, using 60 to 80 c.c. of serum in three or four doses. Using similar amounts of lyophile serum, Scheinblum and Bullowa[10] had good results in 52.1 per cent of patients and moderate results in 26 per cent. Both of these groups felt that hyperimmune serum was an excellent adjunct to sulfadiazine in the treatment of pertussis associated with pneumonia. On the other hand, Frank and co-workers,[11] using much smaller doses of hyperimmune serum, stated that it had no effect on pneumonia complicated with pertussis when used alone. Their mortality rate in patients with pertussis and pneumonia, treated by serum, was 20 per cent. Felton[12] has comprehensively reviewed the literature on the subject.

The value of the sulfonamides in the treatment of whooping cough and its complications has also been investigated. Bradford and associates[13] con-

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*The hyperimmune gamma globulin used in this study was "Hypertussis" kindly supplied by Cutter Laboratories.

sidered sulfadiazine to be of some value when used in conjunction with immune rabbit serum in the treatment of experimental murine pertussis. Litter and co-workers[14] found sulfapyridine to be effective in pertussis pneumonia. However, Kohn and associates,[15] as well as Frank and associates,[11] stated that sulfapyridine had little or no effect on pneumonia complicating whooping cough. The latter investigators, on the other hand, obtained improvement with sulfathiazole in 80 per cent of patients suffering from pneumonia and complicating pertussis. The mortality rate in the group treated by sulfathiazole was 4.0 per cent.

## METHOD

This study represents an effort to assay the value of hyperimmune pertussis gamma globulin in the treatment of uncomplicated pertussis, as well as the worth of hyperimmune globulin and sulfadiazine used in combination for the treatment of pneumonia complicating pertussis. Because of the extreme difficulty in establishing an adequately controlled study of such therapeutic agents, this investigation is limited to the youngest age groups, in whom a high mortality rate would ordinarily be expected. The average age of the entire group was 8.7 months; only nine patients were over one year of age.

Although bacteriologic proof of pertussis was lacking in many instances, no patient was included in this series who did not manifest a typical paroxysmal cough and an absolute lymphocytosis of abnormal degree for his age. In some instances the lymphocytosis was absent or borderline at the time of admission but became apparent later. In addition, most patients exhibited other classical evidences of whooping cough such as whoop, vomiting, and puffy eyes. The diagnosis of pneumonia was made with as much conservatism as possible on the basis of unequivocal physical findings. In fifteen of the patients with pneumonia this diagnosis was confirmed by X-ray examination, although it is realized that a discrepancy between the roentgenologic findings and clinical picture may exist.[16] The remaining patients with pneumonia were too ill to be moved to the x-ray department.

On entry to the hospital, the severity of the illness was estimated on the basis of general appearance, dyspnea, fever, pulmonary involvement, and degree of lymphocytosis. On this basis the patient was assigned arbitrarily to a numerical group numbered from 1 to 5 in ascending severity. Estimation of progress was based on observation of general condition, frequency and severity of paroxysms and vomiting, fluctuations in body weight, and degree and duration of fever. In most patients, serial white blood cell counts and differential smears were done. An attempt was made to determine the day of onset of the disease and the time interval following treatment when definite improvement began. Again, on discharge, the apparent response to treatment was designated as excellent, good, moderate, equivocal, or poor.

The pertussis hyperimmune gamma globulin was obtained by fractionating the pooled plasma of hyperimmunized adult donors, according to the method of Cohn.[17] The donors were required to have a blood agglutination titer of at least 1:1,280 before bleeding, and the resultant redissolved gamma globulin was

required to have an agglutinating titer of 1:15,000 or more. In most patients, 2.5 c.c. of this material were injected intramuscularly on each of four successive days, a total dose of 10 c.c. All patients with pneumonia were also treated with sulfadiazine in a dose of approximately 130 mg. per kilogram per day. When necessary, sodium sulfadiazine was administered parenterally. No significant untoward reactions were noted to the hyperimmune globulin, and only occasional instances of sulfonamide intoxication occurred. All patients received supportive treatment as required, including oxygen, blood transfusions, parenteral fluids, tube feedings, and sedative and expectorant mixtures.

### PERTUSSIS AND PNEUMONIA GROUP

Twenty-six infants suffering from whooping cough complicated by pneumonia at the time of hospital entry were treated with hyperimmune gamma globulin in combination with sulfadiazine. The average age of this group was 7.9 months. The average severity of the disease in these patients at the time of hospitalization, based on a scale of ascending severity of 1 to 5 was 4.0.

TABLE I. RESULTS OF TREATMENT OF PERTUSSIS WITH HYPERIMMUNE GAMMA GLOBULIN

| | UNCOMPLICATED | | PNEUMONIA (WITH SULFADIAZINE) | | TOTAL | |
|---|---|---|---|---|---|---|
| RESULT | NO. | % | NO. | NO. | % | % |
| Excellent | 14 | 50.4 | 2 | 7.7 | 16 | 30.8 |
| Good | 4 | 15.4 | 9 | 34.7 | 13 | 25.0 |
| Moderate | 4 | 15.4 | 7 | 27.0 | 11 | 21.2 |
| Equivocal | 4 | 15.4 | 5 | 19.3 | 9 | 17.3 |
| Worse | 0 | 0.0 | 1 | 3.9 | 1 | 1.9 |
| Died | 0 | 0.0 | 2 | 7.7 | 2 | 3.9 |

Many of the patients appeared almost moribund and experienced observers were frequently amazed at their survival. Twenty-two of the twenty-six patients were febrile (over 100° F. by rectum) and the average duration of fever was 4.4 days. The response to treatment (See Table I) was considered excellent in two, good in nine, moderate in seven, equivocal in five, and one patient became worse after treatment was begun, although he later recovered. Two patients in this group died, a gross mortality rate of 7.7 per cent. One death occurred in an infant who entered the hospital in a terminal state and died eight hours later after receiving only 2.5 c.c. of serum and one dose of sodium sulfadiazine. The other fatal case occurred in an infant who appeared to be doing well but suddenly aspirated vomitus and expired. Autopsy examination revealed death to be due primarily to aspiration and asphyxia. Neither of these deaths could be strictly attributed to failure of therapy. The response to treatment was often dramatic so far as general appearance and defervescence were concerned, but in most instances paroxysmal cough and whoop disappeared more gradually.

### UNCOMPLICATED PERTUSSIS GROUP

Twenty-six patients suffering from pertussis which was uncomplicated at the time of hospital admission were treated with hyperimmune gamma globulin

without sulfonamides. The average age of this group was 9.4 months. Only nine of the twenty-six patients were febrile and the average duration of fever in these patients was 2.8 days. The average numerical severity of this group, using the same arbitrary classification as in the pneumonia series, was 2.7. Results of treatment were considered excellent in fourteen, good in four, moderate in four, and equivocal in four. No patient became worse or died. Very striking was the fact that no patient in this group developed pneumonia or any other complication of pertussis, although several were temporary feeding problems. Symptomatic results, that is, rapid diminution of cough, whoop, and vomiting, were more notable in this group than in the pneumonia series, but again, the effect on mortality and complications was superior to the relief of symptoms.

## DISCUSSION

Great difficulty was encountered in taking into account and weighing properly all possible factors in assigning a certain end result in each given patient. Obviously, since treatment was initiated at the time of hospital entry, which occurred in all stages of the disease, spontaneous improvement was often indistinguishable from that produced by treatment. The average estimated duration of the disease until hospitalization was 11.7 days. Spontaneous improvement in pertussis might be expected to occur, on the average, after the twenty-first day of illness. Consequently, in order to determine whether symptomatic improvement was due to treatment, and at what stage of the disease the hyperimmune globulin might be expected to be most valuable, the entire series was divided into an early and a late group. Twenty-five patients were treated within seven days of the first observed symptom and twenty-seven patients were treated eight or more days after the apparent onset of the disease. The average interval between the initiation of treatment and the day when distinct improvement was first noted was identical in both groups, namely 5.8 days. This would signify that the early group, on the average, began to improve before the thirteenth day of the disease. On the other hand, in the group treated late the average day of improvement falls into the period when spontaneous changes for the better might ordinarily be expected. For this reason symptomatic improvement in late cases following treatment must be largely discounted. That none of these late cases developed complications, however, remains of significance. Several patients in the pneumonia group had not developed their complication until relatively late in the course of their disease.

A more objective measurement of improvement might be found in diminution of the absolute lymphocytosis. This reaches its average maximum on the seventh week following exposure[18] or approximately five or six weeks following the first symptom in untreated patients. In twenty-eight patients in this series, white blood cell counts and differential smears were repeated once or more often during the week following initiation of treatment. In twenty-two patients (79 per cent) a significant decrease in the number of circulating lymphocytes was noted during the first seven days. This often occurred within two or three days, but rarely was the lymphocytosis entirely abolished this rapidly. Six patients,

four of them early in the course of their illness, had an increase in their lymphocytosis within the first week of treatment.

Comparison of the estimated severity on entry and the graded end result revealed that the more severely ill patients manifested slower and poorer symptomatic response than those with mild pertussis. However, this fact also is at least partly a function of duration of the disease before treatment.

## CONCLUSIONS

1. In young infants suffering from pertussis, hyperimmune gamma globulin appeared to shorten the course, lessen the severity, and reduce the rate of complications.

2. Hyperimmune globulin in combination with sulfadiazine appeared to affect favorably the mortality rate of pertussis complicated by pneumonia.

3. The maximum therapeutic effect of hyperimmune gamma globulin was obtained in patients treated during the first seven days of illness.

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# RESTORATION OF DIPHTHERIA IMMUNITY WITHOUT INJECTIONS (BOUSFIELD'S METHOD)

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IT IS well known that local and systemic reactions may occur in older school children and adults when diphtheria toxoid alum precipitated is injected. The occurrence of such reactions has prompted several investigators to seek means of immunization other than by injections. Lowenstein[1] and Vollmer and Wegman[2] used diphtheria toxoid percutaneously. The latter authors obtained evidence of stimulation of antitoxin in less than 25 per cent of the treated group and concluded that percutaneous administration of "booster" doses of toxoid is not a practical procedure. Jensen[3] and Phair[4] instilled diphtheria toxoid into the nostrils. When used as a "booster" dose, this method of administration stimulated good antitoxin responses. However, it produced severe rhinitis in some of the individuals treated and was rather impractical. Bousfield and King-Brown[5] reported that deep inhalation of the air of a room that was impregnated with finely atomized diphtheria toxoid was capable of producing an excellent rise in the antitoxin titer of the blood. The subjects, however, became highly sensitized and developed allergic symptoms. The method was abandoned.

Bousfield[6] then introduced a new concept that of applying antigenic stimuli to the upper portion of the alimentary tract. Gelatin pastilles containing about 100 Lf units of toxoid were sucked by volunteers using a prescribed dosage. Very striking rises in the antitoxin content of the serum occurred in those subjects that had been previously immunized. There was no evidence, however, that the method provided an adequate stimulus for primary immunization. Bousfield suggested that further work should be done by others to verify his results and to determine whether the method is applicable in the case of other antigens such as tetanus toxoid.

The present investigation was undertaken to determine whether Bousfield's findings could be confirmed.

## MATERIALS AND METHODS

*Diphtheria Toxoid.*—At the beginning of our work, the decision was made to incorporate the toxoid into a hard, compressed tablet instead of the gelatin pastille used by Bousfield. This change was made with the thought in mind that stability would be increased and that possible growth of molds would be completely eliminated. This decision made it necessary to use purified and concentrated toxoid.

Fifteen liters of toxoid containing 34 Lf units and 2.72 mg. of nitrogen per cubic centimeter were purified and concentrated by a method that involved adjustment of pH and precipitation by ethyl alcohol in the cold. The yield was 400 c.c., containing about 1,000 Lf units, and 2.64 mg. of nitrogen, per cubic

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centimeter. A sample was diluted to 50 Lf units per cubic centimeter. Groups of 10 guinea pigs were injected with 0.5 c.c. and with 1.0 c.c. After forty-two days, the animals were challenged with 10 m.l.d.'s of toxin. All animals survived.

The remainder of the concentrated toxoid (380 c.c.) was incorporated into compressed tablets, each containing the following ingredients:

| | |
|---|---|
| Diphtheria toxoid | 100 Lf units |
| Sucrose, powdered | |
| Acacia, powdered | |
| Methyl salicylate | |
| Calcium stearate | |

The die used was ½", with standard curvature punches. The weight of the tablet was 12.5 gr. The yield was 3,600 tablets.

A definite number of tablets was allowed to disintegrate in physiologic salt solution and in distilled water. The suspensions were centrifuged. All attempts to determine the number of Lf units in the supernatant were unsuccessful. There was evidence that the toxoid combined with the antitoxin since the tubes became cloudy, but no flocculation took place. Five tablets were allowed to disintegrate in 25 c.c. distilled water and 2.0 c.c. amounts of the suspension were injected into each of six guinea pigs. They were challenged thirty days later with 10 m.l.d.'s of toxin. All the animals survived. This indicated that granulation and compression had not destroyed the potency of the toxoid and that failure to observe flocculation was due to the presence of some inhibiting substance in the tablets.

*Treated Subjects.*—The subjects selected for treatment fell roughly into two groups: (1) those who had been immunized previously or had at some time come in contact with the disease and (2) Schick-positive individuals who had no previous history of immunization or of exposure to the disease.

The first group received a varied dosage; some were given four tablets daily for seven days; others received three tablets daily for seven days; and the remainder of the group received two tablets daily for seven days. The second group received four tablets daily for seven days. The tablets were placed and kept under the tongue until they disintegrated completely. This took about five to ten minutes.

Each subject was bled before and fourteen days after completion of the treatment.

*Determination of Antitoxin Titers.*—Blood serum titrations were done in guinea pigs, using the Roemer technique.

## RESULTS

The results are shown in Tables I to IV inclusive. In general, the subjects who had received a previous diphtheria antigen or who had been exposed to the disease showed a definite increase in antitoxin titer. In some subjects the increase was very marked. It is also evident that this method of immunization was ineffective in those subjects who apparently never had received a primary stimulus.

TABLE I. CHANGES IN BLOOD SERUM TITERS (DOSAGE = FOUR 100 LF TABLETS DAILY FOR SEVEN DAYS)

| CASE | PREVIOUS IMMUNIZATION OR HISTORY OF DIPHTHERIA | ORIGINAL SERUM TITER (UNITS) | TITER FOURTEEN DAYS AFTER TREATMENT (UNITS) |
|---|---|---|---|
| 1 | Dr. S.; no history of immunization; exposed to disease. | 0.25 | 7.0 |
| 2 | Miss C.; immunized in childhood. | 0.05 | 2.0 |
| 3 | Dr. G.; no previous immunization; exposed to disease; Schick negative. | 0.33 | 10-12 |
| 4 | Miss H.; 22 years old; no history of immunization. | < 0.025 | < 0.025 |
| 12 | J. K.; 8 years old; immunized when six months old. | < 0.05 | 0.1 |
| 13 | T. M., 8 years old; immunized when 9 months old. | < 0.05 | 0.22 |

TABLE II. CHANGES IN BLOOD SERUM TITERS (DOSAGE = THREE 100 LF TABLETS DAILY FOR SEVEN DAYS)

| CASE | PREVIOUS IMMUNIZATION OR HISTORY OF DIPHTHERIA | ORIGINAL SERUM TITER (UNITS) | TITER FOURTEEN DAYS AFTER TREATMENT (UNITS) |
|---|---|---|---|
| 5 | Mr. L.; no history of immunization. | < 0.025 | > 0.05 < 0.1 |
| 6 | Miss F.; exposed to disease in 1938 and passively immunized. | < 0.025 | 0.75 |
| 7 | Dr. P.; no history of immunization; Schick negative. | 0.25 | 2.0 |
| 8 | Dr. B.; nasal diphtheria at 21. | 2.0 | 6.0 |
| 9 | Miss B.; immunized in childhood. | < 0.025 | 0.25 |
| 10 | Miss P.; Schick tested in 1944. | < 0.025 | 0.16 |
| 11 | Mr. B., no history of immunization. | 0.1 | 3.0 |
| 18 | Dr. E.; immunized; Schick positive at time of control bleeding. | < 0.025 | 0.14* |
| 19 | Miss S.; one injection of diphtheria antigen at childhood; Schick positive at time of control bleeding. | < 0.025 | 0.025* |
| 22 | Miss B.; immunized in infancy; Schick positive at time of control bleeding. | < 0.025 | 0.1* |

*The titers in cases 18, 19, and 22 may have been influenced by the Schick test previously made.

TABLE III. CHANGES IN BLOOD SERUM TITERS (DOSAGE = TWO 100 LF TABLETS DAILY FOR SEVEN DAYS)

| CASE | PREVIOUS IMMUNIZATION OR HISTORY OF DIPHTHERIA | ORIGINAL SERUM TITER (UNITS) | TITER FOURTEEN DAYS AFTER TREATMENT (UNITS) |
|---|---|---|---|
| 14 | Master L.; immunized in childhood. | 5.0 | 5.0 |
| 15 | Miss L.; doubtful history of immunization. | 0.025 | 0.1 |
| 16 | Master D.; immunized in childhood. | 1.0 | 2.0 |

TABLE IV. CHANGES IN BLOOD SERUM TITERS (DOSAGE = FOUR 100 LF TABLETS DAILY FOR SEVEN DAYS)

| CASE | PREVIOUS IMMUNIZATION OR HISTORY OF DIPHTHERIA | ORIGINAL SERUM TITER (UNITS) | TITER FOURTEEN DAYS AFTER TREATMENT (UNITS) |
|---|---|---|---|
| 23 to 37 | All adults with no previous history of immunization. All Schick-positive tested thirteen days before control bleeding. | < 0.01 | < 0.01 |

Our results confirm Bousfield's findings, namely, that diphtheria toxoid antigen can pass across the mucous membranes of the upper portion of the alimentary tract. The amount of antigen absorbed, however, was not sufficient to provide an adequate stimulus for primary immunization but was sufficient to act as a "booster" dose in those subjects who had previously reached the Schick negative level in antitoxin production.

The results also indicate that it is not necessary to impregnate the toxoid in a gelatin disc but that it can be incorporated in a compressed tablet. In the form of a tablet, the possibility of mold contamination is avoided and the stability of the toxoid perhaps is enhanced.

None of the subjects who received the tablets complained of inconveniences and no reactions or constitutional symptoms were observed. In administering the material to children, the proper supervision should be exercised to make certain that the tablets are kept under the tongue and sucked slowly. The tablets must not be swallowed since, as Bousfield has shown, the antigen is not effectively absorbed from the gastrointestinal tract.

Of all the methods for nonparenteral re-immunization that have been proposed, this appears to be the most promising. The dosage required is rather large and may influence adversely its practical application. Our results indicate that three tablets daily for seven days possibly are as effective as four tablets daily for seven days. Even with this reduced dosage, 2,100 Lf units, roughly 50 to 100 times that required when toxoid is administered parenterally, are required to provide an adequate stimulus for a "booster" dose. The method may find limited application in dealing with adults, many of whom experience severe constitutional disturbance following the parenteral injection of diphtheria toxoid.

## SUMMARY

1. Diphtheria toxoid antigen can be absorbed effectively by the mucous membranes of the upper alimentary tract.

2. Bousfield's findings have been confirmed. The amount of antigen absorbed is sufficient to act as a "booster" dose but is not sufficient to provide an adequate stimulus for primary immunization.

3. The treatment produces no local or general reactions.

4. Bousfield's method appears to be the most promising of all the nonparenteral methods of re-immunization thus far proposed.

5. The large dosage required (2,100 Lf units) may hinder its practical application.

We wish to thank Mrs. Janet C. Bruffy and Mr. Carl Newman, Biological Control Division, who did the serum antitoxin titrations. We are also indebted to Dr. Leroy J. Wenger, who Schick tested and bled some of the volunteers.

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# THE HEART IN NORMAL INFANTS AND CHILDREN

## Incidence of Precordial Systolic Murmurs and Fluoroscopic and Electrocardiographic Studies

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THIS report is concerned with the cardiac findings in presumably normal infants and children who have been under close medical supervision for an average of five years over the age span of birth to 14 years, many from birth. The 260 children* under observation comprised 137 boys and 123 girls. Each child was examined at least four times annually. Fluoroscopic and electrocardiographic examinations were made at least once a year.

### OBSERVATIONS

*The Precordial Systolic Murmur.*—During the first seven years of life, 251 patients were observed for a total of 1,023 patient years; 131 (52 per cent) of the patients presented precordial systolic murmurs during the period of observation. In 78 per cent of these, the murmur was present each year during one or more examinations. In approximately 20 per cent the murmur was first heard prior to 3 years of age, and in 50 per cent prior to 7 years of age. In 42 per cent (fifty-five patients) the murmur was localized to the second and third interspaces. In the remainder, the murmur was heard over the apex or over the entire precordium. The character of the murmur varied on successive examinations; frequently it was musical or soft blowing, at times harsh.

During the age span of 8 to 14 years, sixty-seven children were observed for a total of 241 patient years;† forty-four or 66 per cent of the patients presented systolic murmurs during the period of observation. In 58 per cent the murmur was present each year during one or more examinations. The majority (82 per cent) of the patients presenting murmurs in the first seven years of life retained these murmurs in subsequent years (up to the age of 14 years) (Fig. 1).

*Cardiac Silhouette as Determined by Fluoroscopy.*—The children were examined in the posterior-anterior and oblique views, using a turntable.[1, 2] The cardiac configuration was normal in the posterior-anterior position. In children under 3 years of age, the silhouette was frequently transverse. Abnormal pulsations were not noted. In 90 per cent of the patients, the angle of clearance of the left ventricle was 50 degrees ± in the left anterior oblique position.

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*The 260 patients were selected from a large group (416 patients from 250 families), who were under observation as part of a genetic study. The 156 patients were excluded for the following reasons: fifty-six because of insufficient data; twenty-two because of rheumatic heart disease; twenty-one because of congenital cardiac anomalies; thirty-nine because of equivocal symptoms (episodes of joint pain, epistaxis, and fever); thirteen because of chronic illnesses or anemia; five because of cardiac enlargement alone, as demonstrated by fluoroscopy. Electrocardiographic tracings taken in the course of or subsequent to severe infections or contagious diseases were not included.

†Fifty-eight of these children were observed during the first seven years as well.

Ten per cent of the patients, particularly obese children with high diaphragms, showed sporadic angles of clearance of 55 degrees. In the right anterior oblique view none of the patients showed enlargement of the left auricle (absence of retrodisplacement of the esophagus using barium). There was no significant difference in fluoroscopic findings in children with or without murmurs.

*Electrocardiogram.*—Average values have been defined (three leads) for:

a. P-R intervals;
b. P waves, amplitude and duration;
c. T waves, amplitude;
d. QRS complexes, amplitude and duration;
e. Q-T interval.

*a. P-R Interval.*—Table I summarizes the P-R interval at various ages and rates. Since analysis revealed no significant differences in the average P-R interval for patients with or without murmurs, the data were combined. The average P-R interval was 0.14 ± 0.02 second. It will be noted that the value is 0.12 ± 0.02 second in the first year of life, and 0.13 ± 0.02 second during the age span of 1 to 3 years with pulse rates over 130 per minute.

TABLE I. UPPER LIMIT OF P-R INTERVAL* (927 TRACINGS, 260 NORMAL SUBJECTS)

| AGE (YR.) | RATE | | | | | NO. TRACINGS |
|---|---|---|---|---|---|---|
| | BELOW 70 | 71-90 | 91-110 | 111-130 | OVER 130 | |
| 0-1 | – | – | – | 0.12 | 0.12 | 64 |
| 1-3 | – | – | 0.14 | 0.14 | 0.13 | 299 |
| 3-7 | – | 0.14 | 0.14 | 0.14 | 0.14 | 385 |
| 7-14 | 0.14 | 0.14 | 0.14 | – | – | 179 |

*Standard deviation = ± 0.02 second.

About 6 per cent of the patients without murmurs presented sporadic P-R intervals in excess of the average values. The prolongation equaled or exceeded twice the standard deviation in 2 per cent. About 12 per cent of the patients with murmurs presented sporadic P-R intervals in excess of the average value. The prolongation equalled or exceeded twice the standard deviation in 4 per cent. In both groups, no patient was found to have a P-R interval greater than 0.20 second. It is of some interest that a greater percentage of prolonged P-R intervals was found in the group presenting murmurs, though the average values were not significantly different (Table II).

Examination of 888 tracings with two or more consecutive readings from birth to 14 years of age revealed P-R interval fluctuations greater than 0.02 second in 42 per cent of the patients (representing 52 per cent of the tracings). Eight per cent showed fluctuations greater than 0.04 second.

Table III presents average values for the duration and amplitude of P waves, QRS complexes, and the amplitude of T waves in three leads.* Table IV presents a summary of unusual features found in the 927 tracings.

*Inasmuch as significant differences were not revealed in the patients presenting murmurs and the patients without murmurs, the data have been combined.

The significant limits of the P and T waves and QBS complexes were found by adding or subtracting twice the standard deviations to the average value for amplitude and duration.

TABLE II. PER CENT OF P-R INTERVALS ABOVE THE UPPER LIMITS OF NORMAL (927 TRACINGS, 260 NORMAL SUBJECTS)

| AGE (YR.) | TRACINGS | | PATIENTS | |
|---|---|---|---|---|
| | NO. | PER CENT | NO. | PER CENT |
| *Patients Without Murmurs (123)* | | | | |
| 0-1 | 31 | 9.7 | | |
| 1-3 | 134 | 3.7 | | |
| 3-7 | 100 | 1.0 | | |
| 0-7 (Total) | 265 | 3.4 | 7 | 5.7 |
| 8-14 (Total) | 39 | 0.0 | – | – |
| *Patients With Murmurs (137)* | | | | |
| 0-1 | 33 | 9.0 | | |
| 1-3 | 165 | 6.1 | | |
| 3-7 | 285 | 6.0 | | |
| 0-7 (Total) | 483 | 6.2 | 16* | 12.2 |
| 8-14 (Total) | 140 | 8.6 | 5† | 10.2 |

*Based on 131 patients.
†Based on forty-nine patients who reached 8 to 14 years.

TABLE III. AVERAGE VALUES FOR DURATION AND AMPLITUDE OF P WAVES, QRS COMPLEXES, AND AMPLITUDE OF T WAVES (927 TRACINGS, 260 PATIENTS; BIRTH TO 14 YEARS OF AGE)

| | $P_1$ | $P_2$ | $P_3$ | $T_1$ | $T_2$ | $T_3$ | $QRS_1$* | $QRS_2$* | $QRS_3$* |
|---|---|---|---|---|---|---|---|---|---|
| Average height (mm.) | 1.0 | 1.3 | 0.6 | 2.6 | 2.9† | 0.4 | 11.0 | 12.5 | 10.5 |
| Standard deviation | ± 0.3 | ± 0.5 | ± 0.5‡ | ± 0.9 | ± 1.1 | ± 1.1‡ | ± 4.0 | ± 4.0 | ± 5.0 |
| Average width (sec.) | 0.05 | 0.06 | 0.05 | -- | -- | -- | -- | 0.06 | -- |
| Standard deviation | ± 0.01 | ± 0.01 | ± 0.01 | -- | -- | -- | -- | ± 0.01 | -- |

*Average height and standard deviation derived from 259 tracings.
†$T_2 = 3.7 \pm 1.0$, 8-14 years of age.
‡Standard deviation derived from 490 tracings.

*b. Amplitude and Duration of the P Waves.*—The upper limits (average value plus twice the standard deviation) of amplitude of the P waves were 1.6, 2.3, and 1.6 mm. in Leads I, II, and III, respectively. Slightly over 2 per cent of the tracings showed amplitudes above these limits in Lead II; in these the P waves were usually sharp or peaked. Notching was present in varying degrees at the apex in $P_1$ and $P_2$ in 2 per cent of the tracings. The lower limits of the P waves were 0.4, 0.3 and –0.4 mm. in Leads I, II, and III, respectively. A small percentage (0.5 per cent) showed flat P waves in the first two leads.

The upper limits of duration of the P waves were 0.07, 0.08 and 0.07 second in Leads I, II and III respectively. About 0.5 per cent of the tracings indicated increased duration of the P waves in Lead II.

*c. Amplitude of the T Waves.*—The upper limits of the amplitude of the T waves were 4.4, 5.7 (5.1 in the first seven years of life), and 2.6 mm. in Leads I, II, and III, respectively. A small percentage of tracings showed high $T_2$ waves. The lower limits of the T waves were 0.7, 1.7 (0.7 in the first 7 years), and –1.8 mm. in the three leads. About 1.5 per cent of the tracings showed flat T waves in Leads I and II. Deviation of the R-T segments from the isoelectric exceeding 1 mm. in Leads I and II was found in 1 per cent of the tracings.

*d. Amplitude and Duration of the QRS Complexes.*—The average amplitude of the QRS complexes was found to be 11, 12.5, and 10.5 mm. in Leads I,

II, and III, respectively. The standard deviation was 4 to 5 mm. The average duration was $0.06 \pm 0.01$ second. There were no tracings in our patients exceeding the upper limits of duration (0.08 second). However, approximately 3

TABLE IV. DISTRIBUTION OF UNUSUAL SIGNS (927 TRACINGS, 260 NORMAL SUBJECTS; BIRTH TO 14 YEARS OF AGE)

| UNUSUAL SIGNS | | | NO. |
|---|---|---|---|
| $P_1$ | Notched | Slight | 9 |
| $P_1$ | Notched | Moderate | 3 |
| $P_1$ | Low | (0 amplitude) | 2 |
| $P_2$ | Notched | Slight | 1 |
| $P_2$ | Notched | Moderate | 2 |
| $P_2$ | Low | (0 amplitude) | 3 |
| $P_3$ | High | (Over 2.4 mm.) | 20 |
| $P_3$ | Wide | (Over 0.08 sec.) | 4 |
| $P_3$ | Peaked | ------ | 3 |
| $T_1$ | Low | (Under 0.5 mm.) | 5 |
| $T_2$ | Low | (Under 0.5 mm.) | 9 |
| $T_3$ | High | (Over 6.0 mm.) | 3 |
| $T_3$ | Diphasic | (±) | 1 |
| Absent isoelectric $RT_1$ | | | 3 |
| Absent isoelectric $RT_2$ | | | 8 |
| $QRS_1$ slurred, notched, or splintered | | | 9 |
| $QRS_2$ slurred, notched, or splintered | | | 16 |
| Total | | | 101 |
| MULTIPLE UNUSUAL SIGNS (ONE TRACING) | | | |
| $P_1$ | Notched + $P_2$ notched | | 1 |
| $P_1$ | Notched + $P_3$ wide | | 1 |
| $P_3$ | High + wide | | 2 |
| $P_3$ | High + absent isoelectric $RT_2$ | | 1 |
| $T_1$ | Low + $T_2$ low | | 2 |
| $QRS_1$ slurred + $QRS_2$ slurred | | | 1 |
| Absent isoelectric $RT_1$ + $RT_2$ | | | 3 |
| Total | | | 11 |

TABLE V. PER CENT OF UNUSUAL SIGNS (927 TRACINGS, 260 SUBJECTS; BIRTH TO 14 YEARS OF AGE)

| AGE (YR.) | PATIENTS | PATIENTS WITH UNUSUAL SIGNS | | TRACINGS | UNUSUAL TRACINGS | |
|---|---|---|---|---|---|---|
| | | NO. | % | | NO. | % |
| *Murmur Absent* | | | | | | |
| 0-7 | 120 | 21 | 17.5 | 260 | 23 | 8.9 |
| 7-14 | 18 | 3 | 16.6 | 41 | 3 | 7.3 |
| *Murmur Present* | | | | | | |
| 0-7 | 131 | 21 | 16.0 | 491 | 49 | 10.0 |
| 7-14 | 49 | 10 | 20.4 | 135 | 15 | 11.1 |
| 0-14 (Total) | 260 | 47 | 18.0 | 927 | 90 | 9.7 |

TABLE VI. DETERMINATION OF AVERAGE CORRECTED Q-T INTERVAL* (927 TRACINGS, 260 PATIENTS)

| AGE (YR.) | NO. PATIENTS | NO. READINGS | K (MEAN) SEC. | STANDARD DEVIATION SEC. |
|---|---|---|---|---|
| *Murmur Absent* | | | | |
| 0-7 | 120 | 259 | 0.38 | ±0.02 |
| 7-14 | 18 | 41 | 0.37 | ±0.02 |
| *Murmur Present* | | | | |
| 0-7 | 131 | 492 | 0.37 | ±0.02 |
| 7-14 | 49 | 135 | 0.37 | ±0.02 |

*K in Bazett's Formula, $QT = K\sqrt{\text{cycle length}}$.

per cent of the records showed varying degrees of slurring, notching or splintering of the QRS complexes in Leads I and II. The predominant aberration in the first lead was moderate slurring or splintering in the down-stroke position. The major aberration in $QRS_2$ was splintering or notching at the base.

About 18 per cent of the patients (representing 10 per cent of the tracings) presented sporadic aberrations during the period of observation, exclusive of the number with increased P-R intervals (Table V). A small number demonstrated two aberrations in one tracing (Table IV).

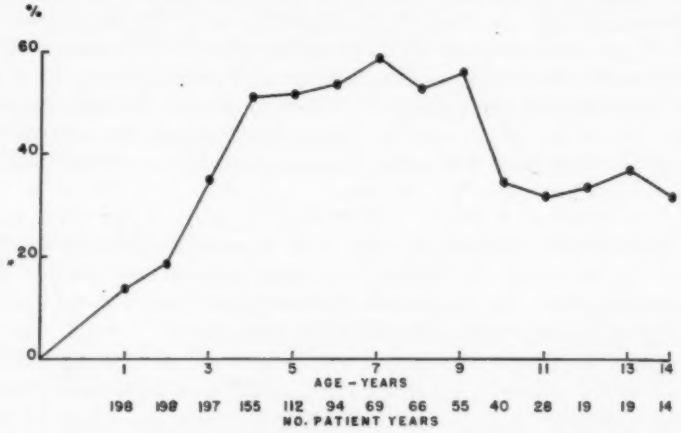


Fig. 1.—Age incidence of precordial systolic murmurs in normal infants and children (1,264 patient years).

*e. Q-T Interval.*—Table VI gives the mean corrected Q-T interval (K in Bazett's formula) in the first fourteen years of life. The value was found to range from 0.37 to 0.38 second. The standard deviation was 0.02 second. Only 1 to 2 per cent of the patients had sporadic corrected Q-T intervals greater than the mean value plus twice the standard deviation. Varying degrees of right axis deviation was found in 16 per cent of the 927 tracings, while 3 per cent showed left axis deviation.

## COMMENT

The frequent occurrence of benign precordial, systolic murmurs of unknown origin is well recognized.[3-5] The occurrence of systolic murmurs in about 50 per cent of our patients in the absence of structural organic heart disease is significant. Contrary to the reports of some observers, the character, location, and transmission of murmurs heard in over half the group were indistinguishable from those of the murmur of mitral insufficiency.[6, 7] It is of interest that in a large majority the murmur, once heard, persisted during the span of observation.

It is significant that in patients observed from birth to 14 years of age, the limits of amplitude and duration of the P waves and QRS complexes, as well

as the amplitude of T waves, correspond closely with established standards.[8-11] However, it is important to note that 18 per cent of "normal" children present tracings with unusual signs or aberrations. This finding emphasizes the caution which must be exercised in the interpretation of electrocardiograms. Of interest is the finding of a similar percentage of "abnormal" tracings in a recent study of 500 healthy flying personnel.[12]

The average P-R intervals at various age levels and rates differ somewhat from hitherto established values. The P-R interval was found to be 0.14 ± 0.02 except during the first year of life, and during the age span of 1 to 3 years with rates over 130 per minute. During the latter age spans, slightly lower values were obtained. It is significant that 6 per cent of the patients without murmurs presented sporadic P-R intervals in excess of the average values, as contrasted with 12 per cent of the patients with murmurs. In both groups, one third of the P-R prolongations equaled or exceeded twice the standard deviation. It is also noteworthy that successive tracings showed P-R interval fluctuations greater than ±0.02 second in more than 50 per cent of the tracings.

## SUMMARY

1. The physical signs, fluoroscopic, and electrocardiographic findings are described in a group of 260 presumably normal infants and children observed during the first fourteen years of life for a total of 1,264 patient years. The average period of observation was about five years.

2. During the first seven years of life, over 50 per cent of the patients presented precordial systolic murmurs. The murmur was heard each year in one or more examinations in 78 per cent. During the age span of 8 to 14 years, 66 per cent of the children presented murmurs. The murmur was heard each year in 58 per cent. Eighty-two per cent of the patients presenting murmurs in the first seven years of life retained these murmurs in subsequent years (up to the age of 14 years).

3. The cardiac silhouette was examined in the posterior-anterior and oblique views. The configuration was normal in the posterior-anterior view. In the left anterior oblique view, the angle of clearance of the left ventricle was 50 degrees ± in 90 per cent of the patients. In 10 per cent, sporadic angles of clearance of 55 degrees were observed, especially in obese children with high diaphragms. In the right anterior oblique position, none of the patients showed evidence of left auricular enlargement (absence of retrodisplacement of the esophagus using barium).

4. A total of 927 electrocardiographic tracings were studied. Average values were obtained for the P-R interval (correlated with age and rate), the duration and amplitude of the P waves and QRS complexes, and for the amplitude of the T waves in the three leads. The corrected Q-T interval was obtained. Significant statistical differences were not obtained by comparison of patients with and without murmurs at various age levels.

a. The P-R interval was found to be 0.14 ± 0.02 second. During the first year of life it was 0.12 ± 0.02 second. During the age span of 1 to 3 years

with rates over 130 per minute, it was $0.13 \pm 0.02$ second. Six per cent of the patients without murmurs showed sporadic P-R intervals greater than the upper limits. Twelve per cent of the patients with murmurs showed P-R intervals greater than the upper limits. In both groups, one third of the P-R prolongations equaled or exceeded twice the standard deviation. Forty-two per cent of the patients (representing 52 per cent of the tracings) showed fluctuations in consecutive P-R intervals greater than 0.02 second.

b. The upper limits of amplitude of the P waves were 1.6, 2.3, and 1.6 mm. in Leads I, II, and III respectively. The lower limits of the P waves were 0.4, 0.3, and –0.4 mm. in the three leads. The upper limits of duration of the P waves were 0.07, 0.08, and 0.07 second in Leads I, II, and III, respectively.

c. The upper limits of the amplitude of the T waves were 4-4, 5.7 (5.1 in the first seven years of life), and 2.6 mm. in Leads I, II, and III, respectively. The lower limits of the T waves were 0.7, 1.7 (0.7 in the first seven years), and –1.8 mm. in the three leads.

d. The average amplitude of the QRS complexes was found to be 11, 12.5, and 10.5 in Leads I, II, and III, respectively. The standard deviation was 4 to 5 mm. The upper limits of the duration of $QRS_2$ was 0.08 second.

e. The corrected Q-T interval (K in Bazett's formula) was found to range from 0.37 to $0.38 \pm 0.20$ second.

About 18 per cent of the patients presented sporadic electrocardiographic aberrations. These represented 10 per cent of the tracings. One half of the aberrations were P-wave changes. The remainder were divided between QRS and T-wave changes.

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# EOSINOPHILIC GRANULOMA OF BONE AND HAND-SCHÜLLER-CHRISTIAN DISEASE

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THREE related clinicopathologic manifestations of disease processes affecting the reticulo-endothelial system have received considerable attention in the recent medical literature. The recognized manifestations have been categorized under three headings: that of eosinophilic or destructive granuloma of bone, that of Letterer-Siwe disease or nonlipoid reticulo-endotheliosis, and that of Hand-Schüller-Christian disease or idiopathic xanthomatosis.

In 1893, Hand[11] described a "peculiar case" of a boy 3 years old with "tuberculosis and polyuria." This case, on later consideration, has been classified under the so-called idiopathic xanthomatoses. In 1915, Schüller[19] recognized, on roentgen studies of bone, certain osseous defects of the calvarium, which he noted to be associated with exophthalmos and diabetes insipidus; he gave the first description of this clinical triad. The classical description of the clinical disease as it was then recognized was made by Christian[2] in 1919, at which time he believed that he was dealing with a disease entity probably due to endocrine dysfunction.

The prevalent view, which classifies the disease as a primary disorder of lipoid metabolism later associated with proliferation of the reticulo-endothelial cells and storage of cholesterol within these cells, analogous to the kerasin storage of Gaucher's disease and the phosphatide storage of Neiman-Pick's disease, was introduced by Rowland in 1928. His hypothesis was that the cholesterol esters were deposited in the tissues and that by acting as foreign bodies they stimulate and cause proliferation of the reticuloendothelial cells. This theory was postulated in spite of the fact that the proliferation may occur in some sites without lipoid storage, the blood lipoid level is usually normal, and most of the lipoid is intracellular. It has also been pointed out[10] that in diabetes and nephroses the hypercholesterolemia up to 800 mg. per 100 ml. causes no such storage or proliferation.

In the light of the numerous case reports of Hand-Schüller-Christian disease which exist in the literature, it is now recognized that the diagnosis is not dependent on the presence of the clinical triad of Christian, but may be based on the characteristic pathologic changes in the tissues. The clinical manifestations will depend on the localization of these changes and will exhibit the classic picture only when the pathologic changes occur in certain areas. We have therefore employed the term disease rather than syndrome.

Several of the reported cases have presented transitional features between the recognized categories of Hand-Schüller-Christian disease and Letterer-Siwe

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disease. This latter term for the widespread proliferation of the reticulo-endothelial cells unaccompanied by lipoid storage was introduced by Abt and Denenholz[1] in 1936. They based their classification on a correlation of the publications of Letterer[13] in 1924, describing the pathologic changes, and of Siwe,[21] establishing certain clinical criteria. The idea of the possible basic identity of these two processes was first propounded by Schultz, Wermbter, and Puhl[20] and has been developed further by Flori and Parenti,[5] Freund and Ripps,[7] Glanzmann,[8] Wallgren,[22] Gross and Jacox,[10] Freud Grossman, and Dragulsky,[6] and Lichtenstein and Jaffe.[14] Essentially, these authors agree that, in both instances, proliferation of the reticulo-endothelium due to an unknown cause is the basic change and that lipoid storage is a secondary phenomenon. This is also the conclusion of Farber[3] in regard to eosinophilic granuloma of bone. With some modification, Siwe's criteria for the diagnosis of nonlipoid reticuloendotheliosis are (1) a condition neither hereditary nor familial, with marked splenomegaly, and mild to moderate hepatomegaly; (2) a hemorrhagic tendency expressed in petechial and purpuric eruptions of the skin; (3) generalized lymph gland enlargement, the nodes being discrete and nontender; (4) the presence of destructive bone lesions in localized areas which may be clinically silent, and (5) a progressive anemia of the nonregenerative type, occasionally accompanied by leucopenia or thrombocytopenia. The pathologic changes are seen in the spleen, liver, thymus, lungs, lymph glands, skin, and lymph follicles of the intestine, and consist of necrosis, hemorrhage, massive proliferation of large pale histiocytic cells, an increase in reticulum fibers, and often the formation of giant cells of foreign-body type. The transitional forms include those cases with more protracted clinical course in which considerable storage of lipoid may be seen.

Jaffe and Lichtenstein,[12] in an excellent discussion of these three related conditions, have mentioned transitional forms between Letterer-Siwe disease and eosinophilic granuloma of bone. The latter has been recognized as single or multiple destructive lesions of bone characterized pathologically by the presence of large numbers of eosinophiles in a granulomatous type of lesion. In the early reports of Finzi,[4] Mignon,[15] and Schairer,[18] the differentiation of this lesion from certain bone tumors, including myeloma, was not made. In 1940, Otani and Ehrlich[16] described seven cases of solitary destructive bone lesions which they regarded as being initiated by trauma. Later the same year, Lichtenstein and Jaffe[14] independently published an account of four cases with pathologic descriptions and employed the term "eosinophilic granuloma of bone" as best expressing the peculiarities of the pathologic picture.

Sidney Farber and his associates[3, 9] in 1941 and 1942, reported thirteen cases, and expressed the view that these lesions represented a variant of Hand-Schüller-Christian disease and did not represent a distinct disease entity as had been implied. This hypothesis has been adopted by Jaffe and Lichtenstein[12] in their comprehensive review.

The following case represents a transitional form between eosinophilic granuloma of bone and Hand-Schüller-Christian disease, suggested both by the clinical course and by examination of biopsy material on two fairly widely separated dates.

## CASE REPORT

CASE 1.—E. S., a Negro girl, was first seen at the age of 19 months at Bradford Memorial Hospital on Oct. 8, 1940. The chief complaint on entry was swelling of the right side of the jaw of one month's duration. The swelling followed a fall in which the jaw was struck.

The family history was not remarkable. The father and mother were living and well, two sisters were living and well, one sister had been born dead, and one brother had died of pneumonia at the age of 8 months. There was no history of any familial diseases. The patient was a full-term normal infant weighing 6 pounds at birth, apparently in good health; the feeding history was adequate except that no vitamin supplements had been given. She had had no illnesses and the developmental history was entirely normal.

Her present illness began approximately one month before hospital entry, at which time she fell and struck the right side of the jaw. Shortly thereafter, a swelling appeared at the location struck; it increased progressively in size, but there was no complaint of tenderness or pain until one week prior to admission, at which time the patient complained of pain in the jaw. The mother noted at that time that the swelling was more marked. A low-grade fever appeared at this time and the child became very fretful and irritable.

Physical examination on entry revealed a child not acutely ill, with a temperature of 99° F. She appeared normally developed. There was no abnormality of the eyes, ears, nose, or throat except for a slight deviation of the nasal septum. The teeth were in good condition and showed no abnormalities. Some edema was noted along the right mandible and there was slight tenderness to touch. Examination of the neck region revealed a mass in the right submandibular area approximately 3 by 6 cm. in size, firm, not fluctuant, very slightly tender, and attached to the lower and outer margin of the mandible. The mass had a slightly rough surface and apparently did not penetrate the mucous membranes of the mouth. The cervical lymph glands were palpable, the nodes on the right being larger than those on the left. Further examination of the lymph glands revealed a palpable right epitrochlear gland and generalized shotty enlargement of all glands. On examination of the thorax and abdomen, the only abnormal finding was a small umbilical hernia.

Laboratory findings were as follows: urine, normal; blood hemoglobin, 10.4 Gm. per 100 ml.; red blood count, 4,250,000; white cell count, 9,700, and a differential count of 53 segmented forms, 6 bands, 40 lymphocytes, 1 monocyte, and 1 eosinophile. A report of a roentgenogram made on Oct. 12, 1940, states, "A large expanding tumor is present, involving the posterior half of the horizontal ramus and lower portion of the ascending ramus of the right mandible. The lower portions of the tumor extends about one-half inch below the mandible. It appears that the periphery of the tumor has been disrupted in several places, possibly placing it in the classification of malignant tumor." Further studies of the chest and long bones showed no other bone changes. The blood Kline and intradermal tuberculin tests, 1:1000 and 1:100, were both negative.

A preoperative diagnosis of tumor of the mandible, either a dentigerous cyst, adamantinoma, or malignant tumor of bone, was made. At operation on October 25, a tumor was seen eroding the outer surface of the mandible for about 1 inch and also eroding the upper surface and posterior portion of the lower ramus. The tumor mass was removed and with it a small gland attached to the lower surface from the cervical chain. A description of the gross findings in bone and lymph node biopsies is not available. Histologically, the tissue in both the bone fragments and the lymph node was characterized by a granulomatous proliferation of large, pale, sometimes polygonal cells, interpreted as macrophages or histiocytes. The nuclei of these cells were large and vesiculated and some cells were multinuclear. There were many giant cells of the foreign-body type. A striking feature of the microscopic picture was large numbers of eosinophilic leucocytes scattered throughout all the section and in some fields gathered into clusters or sheets. These leucocytes usually presented bilobate and often trilobate nuclei; the cytoplasm was definitely eosinophilic and granular. In addition, there were moderate numbers of neutrophilic polymorphonuclear leucocytes. Examination of the sections failed to reveal vacuolated cells, and, unfortunately, no fat stains

were made on this specimen. The lymph node architecture was still apparent, with numerous small follicles having germinal centers of moderate size, which exhibited no unusual histologic findings. The changes in bone and lymph node were identical in the tissue examined with the exception that the eosinophilic infiltration was more striking in the lymph node. The diagnosis on the first examination was that of solitary or eosinophilic granuloma of the mandible and local lymph node, and this diagnosis was confirmed on reexamination of the original slides.

Fig. 1.—The patient at the time of final entry at the age of 6 years, February, 1945. Note the cervical lymphadenopathy.

Following an uneventful postoperative course, the patient was discharged Nov. 6, 1940, with complete wound healing. The second entry of the patient, at the age of 4 years, occurred Jan. 29, 1944. The interval history was notable for the development of excessive thirst which was first noted one year prior to admission and of which the patient complained constantly. At the same time, great frequency of urination with increase in quantity of urine occurred and enuresis developed. The mother stated that the urine appeared colorless and watery. However, the chief complaints on the second entry were headache, fever, and vomiting of eighteen hours' duration. The child had become ill early the night before entry, with listlessness, slight drowsiness, and low-grade fever, and later that night the fever rose sharply, accompanied by severe headache and many episodes of vomiting. In the early morning, the patient became irrational and was therefore brought to the hospital.

On her admission to the Children's Hospital of Texas, physical examination revealed a well-developed and well-nourished Negro girl who was stuporous and appeared acutely and critically ill, with a temperature of 103.6° F., pulse 100, and respirations 28. The lymph nodes were palpable generally but were larger in the cervical region. There was nuchal and back rigidity and a positive Kernig's sign. The rest of the examination was nonrevealing.

Laboratory findings were as follows: The urine was clear and acid with no abnormal formed elements (specific gravity was not recorded); blood counts showed a mild anemia of 8 to 10 Gm. of hemoglobin, and a white blood cell count of 27,650, with a marked left shift in the differential count. The count had fallen to 7,550 with a normal differential by the time of discharge. The spinal fluid was turbid and contained 13,000 white cells; *Neisseria intracellularis* was seen on a stained smear and obtained on culture.

Therapy with sulfadiazine and adequate fluid was instituted, and the temperature fell to normal by the fourth day. Convalescence was uneventful and rapid, and the patient was discharged in good condition with a diagnosis of acute meningitis due to the meningococcus.

The third entry of the patient occurred on Feb. 5, 1945, at the age of 6 years. At this time, the chief complaint was swelling in the left side of the neck of three or four months' duration, with pain and limitation of motion on the right side of the neck for several hours, following a fall, with trauma to the area.

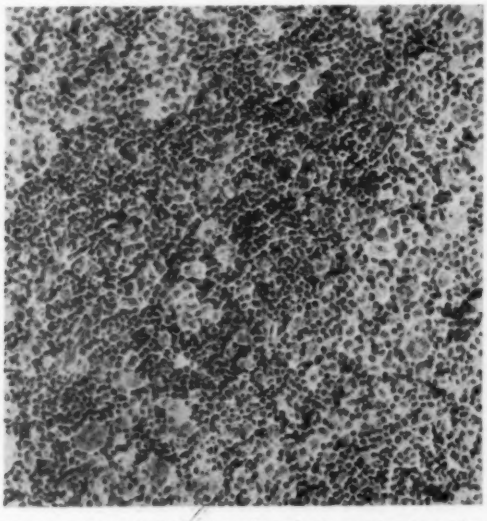

Fig. 2.—Photomicrograph (×120) of lymph node from the first biopsy in 1940, showing hyperplasia of large pale cells, the histiocytes or macrophages. Note the numerous giant cells of foreign body type and the large numbers of dark staining cells, the eosinophiles, which are both scattered through the section and arranged in small clusters.

The interval between admissions was marked by continuation of the habits of excessive consumption of water and excessive urination. According to the child's mother, a gallon container of water was left with the child every night at bedtime and by morning this had been consumed and an approximately equal amount of urine had been passed. During the day she asked for water constantly and urinated constantly. Also in the period between hospitalizations, a mass in the left inguinal region had appeared intermittently and had alternately increased and decreased in size. This mass was tender and the tenderness made it difficult for the patient to walk. After an indefinitely stated period of time, the swelling and tenderness subsided. In February, 1944, the mother had also noted another slightly tender swelling which appeared on the left shoulder blade following a fall; this swelling remained a short while and then disappeared. The masses in the neck noted on the second hospital entry had been constantly present during the interim and were thought to have increased slowly in size for three or four months. In the outpatient clinic, sulfathiazole was given empirically on suspicion of some sort of infectious process, but was without effect.

Two days before admission, the child received a blow to the neck on the left side, following which the mother noticed an acute swelling in the region. The patient began to complain of pain and tenderness to touch; a low-grade fever developed.

Physical examination on entry revealed her to be well-developed and nourished and not acutely ill. Temperature was 100.2° F. The eyes were prominent, but this was thought possibly to be racial and not the results of actual exophthalmos. The lymph nodes were found to be moderately enlarged in the anterior and posterior cervical chains, averaging

from 1 to 3 cm. in diameter, and were moderately painful and tender on palpation. There was slight generalized glandular enlargement, with inguinal nodes 1 to 2 cm. in diameter. Thorax and abdomen were not remarkable except that the liver was palpable just below the right costal margin.

Laboratory findings were as follows: urine, pale and watery in appearance with a specific gravity of 1.002, albumin negative, sugar negative, with no abnormal formed elements; blood, 11.7 Gm. of hemoglobin, red blood cell count of 4,360,000, with white blood cell count of 8,000, and a differential count of segmented forms 61, bands 3, lymphocytes 34, monocytes 1, and eosinophiles 1. The calcium level was 12 mg. per 100 ml., phosphorus 5.85, and phosphatase 3 Bodansky units; blood plasma proteins were 8.8 Gm. per 100 ml., with an albumin of 5.1 Gm. and globulin of 3.7 Gm. Roentgenograms of the chest, skull, pelvis, and long bones did not show any defects of the skeleton.

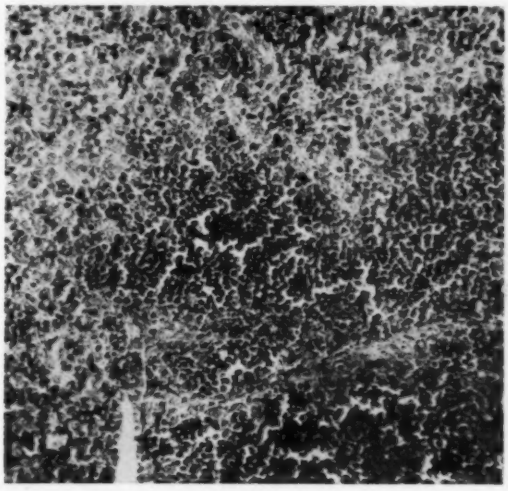

Fig. 3.—Photomicrograph (×135) of lymph node from the second biopsy in 1945, showing proliferation of histiocytes and clusters of eosinophiles. Note the marked resemblance to the first specimen.

In the light of the previous history, Hand-Schüller-Christian disease was suspected preoperatively. At operation, on Feb. 21, 1945, two lymph nodes were removed from the left side of the neck for pathologic examination. The report of lymph node biopsy states: "On gross examination the specimen consisted of two lymph nodes, the larger of which was 1.5 by 1.0 cm. This node was firm on palpation and on section appeared yellowish-red. A second node was present measuring 0.8 by 0.5 cm., also firm and yellowish red."

On microscopic examination, the sections stained with hematoxylin and eosin showed lymph nodes which exhibited moderate fibrous thickening of the capsule and infiltration of the capsule with moderate numbers of lymphoid cells and eosinophiles. The architecture of the lymph node was not destroyed, and numerous follicles were seen, most of which were rather small and lacked germinal centers. A few of the follicles had small germinal centers and the cells of these areas were not unusual. The most remarkable change consisted in extensive proliferation of large, pale, polygonal cells, which had abundant clear or slightly granular pink-staining cytoplasm and an oval vesicular nucleus with a clear nuclear membrane and a prominent nucleolus. Most of these cells appeared free, but some of them appeared to be a part of a reticulum and had the characteristics of reticulo-endothelial cells with irregularly shaped or horseshoe shaped nuclei. Moderate numbers of the cells were seen

to contain small and large vacuoles within the cytoplasm. The proliferation was seen everywhere within the tissue, and the cells filled the lymph sinuses. There was, in addition, a very marked infiltration of the entire tissue with eosinophilic leucocytes, and there were moderate numbers of neutrophilic polymorphonuclear leucocytes and a few lymphocytes in the sinusoidal spaces. Some of the sinusoidal spaces appeared to contain edema fluid and there were several small focal areas of necrosis scattered throughout the node. Sections stained with Sudan IV for fat showed that many of the macrophages contained small fat droplets, some a few and others a large number. Typical foam cells were not seen. On examination of the sections with a polarizing microscope, numerous doubly refractile crystals typical of cholesterol esters were seen. A diagnosis of granulomatous inflammation of lymph nodes, Schüller-Christian type, was made.

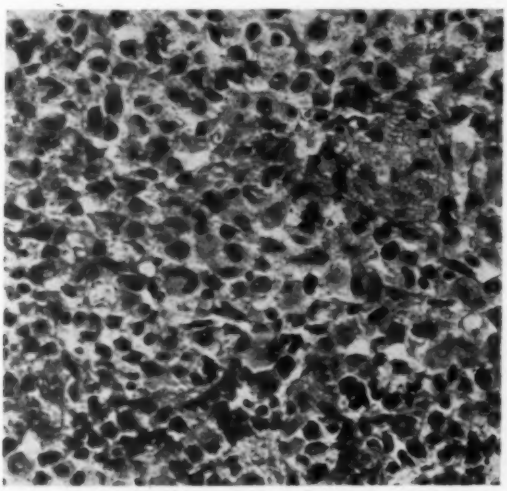

Fig. 4.—Photomicrograph (×160) in higher power to show accumulation of lipoid in the macrophages. Fat stains of the same specimen (when examined under a polarizing microscope) showed doubly refractile crystals of cholesterol esters.

After this diagnosis was confirmed, studies were undertaken to determine the water balance, ability to concentrate the urine, and the effects of pitressin. A concentration test done Feb. 19, 1945, showed inability to concentrate beyond a specific gravity of 1.003 after withholding fluids for twelve hours. The measured fluid intake averaged 2,500 ml., and the output, 2,900 ml. (The discrepancy probably can be explained by the child surreptitiously obtaining extra water, which she did with great cleverness.)

Beginning on March 2, 1945, intramuscular injections of 1 ml. of pitressin tannate in oil were given daily for four days. During this time the average intake decreased to 700 ml. and the output to 600 ml. per twenty-four hours, and the constant thirst disappeared. An attempt was then made to persuade the child to take pituitary powder by nasal insufflation but without success. She was then given three separate irradiations over the nodes in the neck and over the pituitary region, the latter in an attempt to ameliorate the symptoms of diabetes insipidus. When the pitressin tannate injections were discontinued, the average daily intake and output again rose to the neighborhood of 2.5 L. per twenty-four hours. At the time of discharge on March 29, 1945, there were no changes in the symptoms despite therapy.

This patient has not returned to the outpatient clinic for follow-up and her present status is unknown.

## COMMENT

The case reported here most closely resembles that of Freund and Ripps[7] in its later clinical course, in that the involvement was primarily visceral and predominant in the lymph nodes. However, this case presents features of the classical triad of Christian in that there was definite diabetes insipidus and a suggestion of exophthalmos. Although there were no localized lesions of the skeleton demonstrable on the last entry, it is of interest that there was a preceding destructive bone lesion, demonstrated by roentgen examination, which pathologically resembled the later lesion of the lymph node closely except for the absence of lipoid. This suggests a progression of the changes from those characterizing eosinophilic granuloma, which shows no lipoid storage, to the typical Hand-Schüller-Christian type of tissue with foam cells, in the manner postulated by Farber.[3, 9]

In each instance, the granulomatous nature of the pathologic process was very striking, and it is difficult to avoid the assumption that these related clinicopathologic conditions are basically inflammatory in type.

## SUMMARY

1. A brief review of the recent medical literature discussing the relation of the three clinicopathologic conditions of eosinophilic granuloma of bone, Letterer-Siwe disease, and Hand-Schüller-Christian disease, is given.

2. A case report is given of a patient who presented a transitional form of the disease first manifested as eosinophilic granuloma of bone and four years later as Hand-Schüller-Christian disease.

3. The pathologic findings showed a striking resemblance in both instances, except for the presence of anisotropic lipoid in the second biopsy specimen.

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# PETECHIAE IN CHILDREN: INCIDENCE, SEASONAL VARIATIONS, AND ETIOLOGY

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INFORMATION in the literature is scant regarding incidence and pathogenesis of petechiae in children, and nothing appears regarding their seasonal variations. These and related topics are discussed.

A five-year survey was undertaken in various pediatric clinics at the New York Post-Graduate Medical School and Hospital of Columbia University. Counts were made of petechiae seen in children with frequent colds (chest clinic), allergy (allergy clinic), rheumatic symptoms (cardiac research clinic) and in children with a variety of complaints (general clinic). Altogether, counts were made on 503 clinic patients, 170 of whom were rheumatic.

*Area Covered in Count.*—In 333 nonrheumatic children, petechiae were recorded for five areas: left and right upper extremity; chest, back, and head including neck; counts were totaled for each child. In 170 rheumatic children counts were made in only three areas: left and right upper extremity, and head, including neck.

*Repeat Counts.*—In twenty-eight children with frequent colds and eighty-one rheumatic children, counts were repeated at different seasons.

A petechia may be defined as a pinpoint to pinhead red spot formed by the effusion of blood in the skin or mucous membrane.[1] Histologic examination shows dilated small vessels, usually capillaries, just under the epidermis and in the upper and middle layers of the cutis, with only a relatively small amount of free hemorrhage in the surrounding tissues. The dilated vessels are filled with blood imparting the red color.[1]

Petechiae appear in acute and chronic infections. Among the acute conditions are meningitis, Rocky Mountain spotted fever, typhus fever, severe scarlet fever, pneumonia, gonorrheal septicemia, scurvy, allergy, and virus diseases such as smallpox, measles, and German measles. Among the chronic conditions petechiae are encountered in bacterial endocarditis, purpura and leucemia. Petechiae have been observed to appear during menses,[2] with a sudden drop in barometric pressure, and in connection with twitching and athetoid movements of patients with scarlet fever,[3] rheumatic fever, and frequent colds.

Petechiae contain the causative bacteria in meningitis and gonorrheal septicemia;[4] in other diseases, toxins are believed to rupture a vessel wall, as in endocarditis.[5]

## CHILDREN WITH FREQUENT COLDS

Thirty-six children of the chest clinic were observed for petechiae over a five-year period. Many were examined at weekly intervals when they appeared for subcutaneous vaccine prophylaxis against colds.

Three types of vascular lesion other than petechiae were noted in these children. They were (1) telangiectasis, (2) spider nevus, and (3) ecchymosis.

Address delivered June 10, 1947, at Southern Oregon Medical Society, Fifty-sixth Annual Session, Roseburg, Ore.

*Telangiectasis.*—Telangiectases are red vascular dilatations and presumably result from enlargement of pre-existing vascular channels.[6] Sites of predilection are the flush areas of the face, and the lateral surfaces of the nose.[6] Among the thirty-six children with frequent colds, telangiectases appeared in eight. They were only slightly evident and usually single. Less commonly there were two or more telangiectases. Seven of the eight children with telangiectases had at least one associated petechia. Blood platelet counts tended to be low, varying from 70,000 to 350,000 per cubic millimeter. Four of the seven had counts below 200,000. Bleeding time tended to be prolonged, varying from 2.5 to 11 minutes, averaging 4.7 minutes (Duke). The telangiectases were located mainly on the cheeks or back.

*Spider Nevus.*—This is a combination of petechia and telangiectasis. Minute red vessels radiate from the petechiae like the legs of a spider, whence the name. Spider nevi were included with petechiae since the telangiectasis may disappear, leaving only the petechial spot. The usual location of the lesion was on the face, frequently under an eye and less commonly on the nose. Lesions were more often single than multiple. Spider nevi were observed more commonly in the spring than in the fall. When present, spider nevi serve as excellent barometers of the amount of capillary dilatation, being most noticeable at times when capillary resistance, measured in centimeters of mercury suction, is low.

*Ecchymosis.*—There are a number of descriptive terms used in the quantitative and qualitative differentiation of hemorrhage. These terms include petechia, ecchymosis, black and blue spot, and suffusion. In contrast to petechiae, which are red, the others are larger and are usually blue.

In six of the thirty-six children with frequent colds, there appeared during a five-year period two or more ecchymoses associated with insignificant trauma. All six children had at least one associated petechia. One patient, who had from eighteen to forty-two petechiae (uppermost graph in Fig. 1), on more than one occasion had three black and blue spots.

*Twitching.*—Subchoreic twitching was recorded in five patients, and in one of these new petechiae were seen to develop with a return or increase in twitching, suggesting a common factor for both phenomena. This may be bacterial toxin. I previously described the frequency of athetoid movements and subchoreic twitching in scarlet fever patients who had low capillary resistance presumably produced by increased amounts of streptococcus toxin.[3]

*Petechiae and Respiratory Infections.*—In one child, new petechiae appeared with almost every cold. Several children who had developed petechiae for the first time gave a history of a recent cold, tonsillitis, acute bronchitis, or other acute respiratory infection. Often, prior to the development of petechiae, there were symptoms of joint and abdominal pain. Mothers called attention to the development of new petechiae, occasionally noting their appearance during a cold.

*Brightness of Petechiae.*—Petechiae were brighter when of recent origin, as when new ones appeared during a cold. Interesting fluctuations were noted

in size, brightness, and number of petechiae and spider nevi. Factors which seemed to influence these variations were (1) season, (2) changes in weather, (3) menses, and (4) streptococcic activity.

*1. Season* had the most constant influence both on brightness and number of petechiae. Many petechiae, which were readily counted in the spring, were seen with difficulty a few months later in the fall. Judging from the total count, some petechiae had disappeared. Those which were visible in the fall tended to be smaller and paler, that is, more pink than red. Seasonal variations in the number of petechiae during a two-year period are noted in Fig. 1.

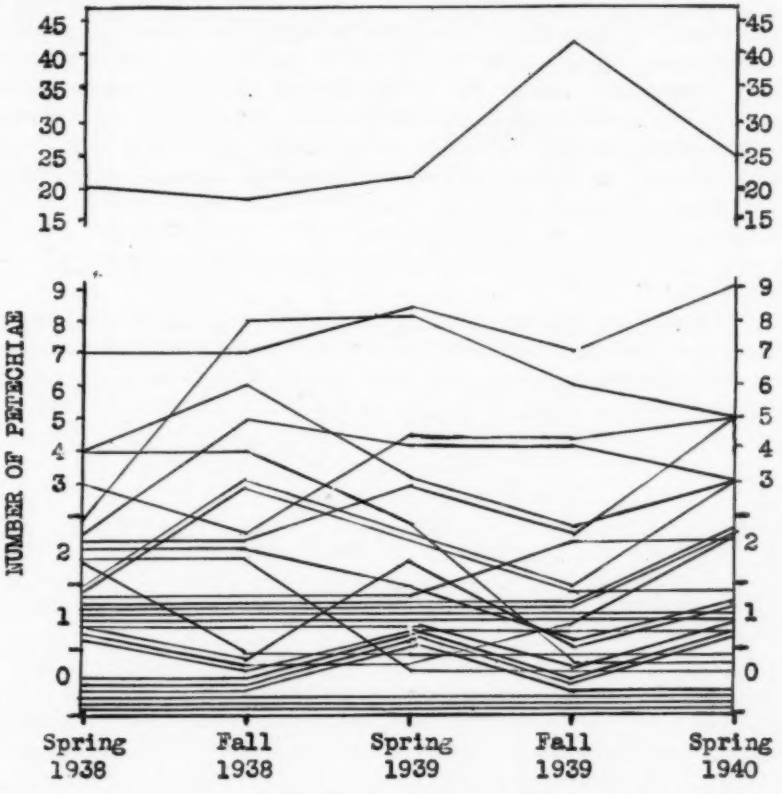


Fig. 1.—Seasonal variations in number of petechiae in twenty-eight children.

Seasonal variations in the number of petechiae in twenty-eight cold-susceptible patients were as follows: from spring, 1938, to fall, 1938, seventeen children showed no change in number, five showed an increase, and six a decrease; from fall, 1938, to spring, 1939, there was no change in twelve, an increase in nine, and a decrease in seven; from spring, 1939, to fall, 1939, no change in twelve, an increase in three, and decrease in thirteen; from fall, 1939.

to spring, 1940, no change in twelve, an increase in thirteen, and a decrease in three. Thus, we note a tendency for petechiae to increase in the spring and decrease the following fall.

During these two years, weather factors may have influenced the seasonal variations in petechiae. The number of petechiae did not vary as much from spring to fall, 1938, as from spring to fall, 1939. Likewise, the fall, 1938, to spring, 1939, variations were less than those noted from fall, 1939, to spring, 1940. The mildness of the first six months (mean daily temperatures totaled 449° F. above normal) of 1938 was in contrast to the severity of the first six months of 1940 (360° F. below normal). One hundred rheumatic patients observed during the same years[7] showed corresponding variations in hemoglobin, values averaging 77 per cent in the mild (1938) and 72.35 per cent in the severe (1940) winter-spring season. We postulated that, because of severe weather (chilling), the resulting anemia may have been produced by increased amounts of streptococcus toxin in the blood. It is possible that toxins may likewise account for variation in the number of petechiae noted during the same seasons.

The patient represented in upper graph (Fig. 1) was a notable exception to the usual seasonal fluctuations. Several "colds," possibly allergic, developed during the summer months of 1939 prior to the increase of twenty petechiae noted in the fall of 1939.

*2. Changes in Weather.*—Among weather factors, barometric pressure changes were followed throughout the study. Barometric pressure on seven occasions declined suddenly more than 0.5 inch on days when petechiae were sought. Petechiae tended to appear bright red at this time. Likewise, on these days, when petechiae were artificially produced with a capillary resistometer using negative pressure (suction), they appeared in greater numbers and at lesser pressures; that is, capillary resistance was lower at this time.[8] Petersen[9] has emphasized the effect of sudden drops of barometric pressure on capillary dilatation. Rentschler and co-workers of the Mayo Clinic[10] called attention to the increased restlessness and pain in rheumatic patients during a drop in barometric pressure, symptoms which might occur with the release of streptococcus toxin from a focus of infection.

*3. Menses.*—Just prior to menses and during the first and second day of the menstrual flow, petechiae and spider nevi were particularly bright, an observation made on girls in the rheumatic state and with frequent colds. In rheumatic girls, capillary resistance was found to average 13.7 cm. in the premenstrual, 14.4 cm. in the menstrual, and 16.7 cm. in the intermenstrual phase.[11]

*4. Streptococcic Activity.*—Several symptoms, suggesting streptococcic activity, were noted coincidentally with an increase in number of petechiae and their brightness. These included colds believed to be caused by the streptococcus,[12] acute tonsillitis, acute bronchitis, and pain in joints, muscles, and abdomen. Streptococcus toxin may have been the responsible etiologic factor for increased twitching and low capillary resistance.[3] In one five-year-old girl, a petechial rash was inadvertently produced by streptococcal toxin, following the injection of a streptococcus filtrate used for prophylaxis against recurrences of rheumatic fever.

## PETECHIAE IN CHILDREN OF THREE CLINICS

Petechiae were counted in 119 children of the general clinic, forty-nine children in the allergy clinic with various manifestations of allergy, and in 165 children with frequent colds in the chest clinic. The percentage of patients showing at least one petechiae in the three clinics was 40, 53, and 60, respectively. The average number of petechiae per patient in the three groups was 0.9, 1.2, and 1.5, respectively (Table I).

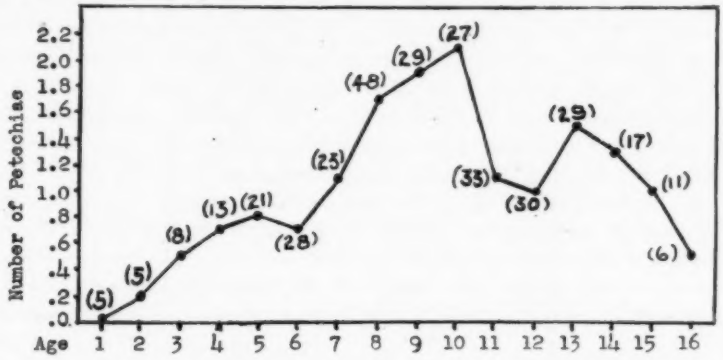


Fig. 2.—Average number of petechiae at various ages in 333 children. (Figures in parentheses represent number of cases.)

The number of petechiae shows a relationship to age, as seen in Fig. 2.

One notes a progressive average increase in number of petechiae from zero at age one to 2.1 petechiae at age 10. A sudden drop in number is noted at age 11 (1.1 petechiae) and age 12 (1.0 petechiae) and a secondary but lesser rise at age 13 to 1.5 petechiae. Thereafter, to age 16, there is a progressive diminution in number to 0.5 petechia. What influences the secondary rise at age 13 could not determined. The possible influence of sex (earlier puberty in females) at this age was ruled out since approximately equal numbers of petechiae were found in boys and girls. In later life (middle and old age), petechiae tend to be larger and more numerous.

The ubiquity of the streptococcus and its toxin may account for the production of petechiae, even in nonrheumatic children, as evidenced by the sudden decline in the number of petechiae from the peak at age 10 to distinctly lower values at ages 11 and 12, corresponding exactly with the known decline in incidence of rheumatic exacerbations at these ages. Regarding rheumatic fever, Cohn and Lingg state: "A curve representing the ages at which reactivations occur shows a sharp decline beginning at the age of 11 or 12."[13] Is it fortuitous or a significant correlation that the diminution in number of petechiae and attacks of rheumatic fever coincide at exactly the same ages? Does streptococcic activity diminish at these ages?

## RHEUMATIC CHILDREN

Petechiae were counted in 170 rheumatic children, and repeated at a later age in eighty-four of these, thus accounting for 254 counts at an average age

TABLE I. NUMBER OF PETECHIAE AT VARIOUS AGES IN PATIENTS OF THREE CLINICS

| | AGE | | | | | | | | | | | | | | | | NO. PATIENTS | AVERAGE NO. PETECHIAE PER PATIENT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | | |
| *General Clinic* | | | | | | | | | | | | | | | | | | |
| No. patients | 5 | 2 | 6 | 8 | 7 | 10 | 7 | 16 | 13 | 10 | 12 | 11 | 5 | 2 | 3 | 2 | 119 | |
| No. petechiae | 0 | 0 | 4 | 3 | 5 | 8 | 11 | 22 | 10 | 11 | 15 | 12 | 4 | 3 | 1 | 0 | | 0.9 |
| *Allergy Clinic* | | | | | | | | | | | | | | | | | | |
| No. patients | – | 2 | 1 | 2 | 1 | 4 | 6 | 10 | 3 | 4 | 4 | 4 | 5 | 3 | | | 49 | |
| No. petechiae | – | 0 | 0 | 1 | 1 | 1 | 2 | 10 | 3 | 5 | 6 | 3 | 19 | 9 | | | | 1.2 |
| *Chest Clinic* | | | | | | | | | | | | | | | | | | |
| No. patients | – | 1 | 1 | 3 | 13 | 14 | 10 | 22 | 13 | 13 | 17 | 15 | 19 | 12 | 8 | 4 | 165 | |
| No. petechiae | – | 1 | 0 | 5 | 12 | 11 | 13 | 52 | 41 | 42 | 16 | 17 | 20 | 10 | 10 | 3 | | 1.5 |
| Total No. patients | 5 | 5 | 8 | 13 | 21 | 28 | 23 | 48 | 29 | 27 | 33 | 30 | 29 | 17 | 11 | 6 | 333 | |
| Total No. petechiae | 0 | 1 | 4 | 9 | 18 | 20 | 26 | 84 | 54 | 58 | 37 | 32 | 43 | 22 | 11 | 3 | | |
| Average No. petechiae per patient | 0.0 | 0.2 | 0.5 | 0.7 | 0.8 | 0.7 | 1.1 | 1.7 | 1.9 | 2.1 | 1.1 | 1.0 | 1.5 | 1.3 | 1.0 | 0.5 | | 1.3 |

TABLE II. NUMBER OF PETECHIAE IN RHEUMATIC CHILDREN AT VARIOUS AGES (COUNTS IN THREE AREAS)

| AGE | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. patients | 3 | 3 | 7 | 10 | 18 | 22 | 13 | 24 | 33 | 30 | 41 | 21 | 19 | 10 |
| Total No. petechiae | 2 | 4 | 10 | 12 | 11 | 35 | 18 | 17 | 24 | 25 | 36 | 15 | 27 | 5 |
| Average No. petechiae per patient | 0.7 | 1.3 | 1.4 | 1.2 | 0.7 | 1.6 | 1.4 | 0.7 | 0.7 | 0.8 | 0.9 | 0.7 | 1.4 | 0.5 |

of 11.3 years. In these rheumatic patients counts were made in only three areas: right and left upper extremity and head. Since in the 333 nonrheumatic children the count was made in five areas, the count in rheumatic patients is excluded in Table I. However, comparisons can be made in the two groups.

In comparing the number of petechiae in rheumatic (Table II) and nonrheumatic children (Table I), if allowance is made for uncounted petechiae on the torso of rheumatic patients, the average count will be found greater in this group. Even without such allowance, the number of petechiae is considerably greater in young rheumatics over nonrheumatics. For example, at age 5, rheumatic children showed an average total of 1.4 petechiae in three areas as compared with only 0.8 petechiae in five areas of the nonrheumatic children. At age 6, the ratio is 1.2 against 0.7 petechiae. The appearance of petechiae in rheumatic children in the early years of life suggests the possible role of streptococcus toxin in their causation.

*Seasonal Variations.*—Counts were made in eighty-one rheumatic patients in the fall and spring. No seasonal change was noted in thirty-seven patients, twenty-eight of whom had no petechiae at either season. Of the remaining forty-four patients, thirty-six showed an increase and eight a decrease in the spring over the previous fall. In these eighty-one rheumatic children the total count of petechiae was forty-eight in the fall and ninety-two in the spring, forty-four petechiae having been acquired through the winter months.

*Blood Platelets.*—As in thrombopenic purpura, deficiency in number of thrombocytes may have influenced the formation of petechiae in rheumatic patients. Platelet counts by the direct citrate method were made in 100 unselected rheumatic fever patients and were under 200,000 per cubic millimeter in 67 per cent. The mean value for the entire group was 184,000 blood platelets per cubic millimeter, with lowest values during April and May of two successive years.[7]

*Capillary Resistance.*—It was thought that a comparison of capillary resistance readings with the count of petechiae during both seasons might shed some light on the possible role of streptococcus toxin in the production of petechiae. It is known that streptococcus toxin lowers capillary resistance. Was it possible to show that those who developed petechiae had a lower capillary resistance than those who either failed to develop petechiae or whose petechiae disappeared? Such a comparison was made but results were negative. Almost all rheumatic children tended to exhibit increased capillary fragility in the spring, regardless of increase or decrease in number of petechiae. Had capillary resistance readings been made on days when petechiae actually appeared, one might have determined definitely whether capillary fragility coincided with the appearance of petechiae. For it is known that capillary resistance is quite variable from time

to time. During illness, as in scarlet fever, capillary resistance may be only 5 cm. at the onset and rise to 30 cm. one week later;[3, 14] during the same period myriads of petechiae seen at the onset in the toxic case may disappear.[3]

## CONCLUSIONS

1. Petechiae are commonly seen in children. At least one petechia was found in 172 of 333 clinic children, an incidence of 52 per cent.

2. The incidence of petechiae in three groups (a) general clinic cases, (b) allergic children, and (c) children with frequent colds, was 40, 53, and 60 per cent, respectively. The average number of petechiae was 0.9, 1.2, and 1.5, respectively.

3. Age variations are noted. From an average of zero (0.0) petechia at age one, the number increases progressively, rising to a peak of 2.1 petechiae at age 10. Fewer petechiae are seen between the ages of 11 and 16.

4. Seasonal variations exist, the tendency being toward an increased number of petechiae in the spring and a decrease in the fall.

5. Petechiae are brighter red under the following conditions: near the menses, with associated rheumatic pain or respiratory infection, during a sudden drop in barometric pressure, and in the spring.

6. The relation of petechiae to spider nevi, telangiectases, spontaneous bruises, twitching, blood platelets, and capillary resistance, is discussed.

7. Streptococcus toxin is probably responsible for many petechiae which appear "spontaneously." Careful history reveals that they appear with, or immediately after, respiratory infections (colds, tonsillitis, bronchitis) and joint and muscle pains. Petechiae appear at an earlier age and in greater numbers in rheumatic as compared with nonrheumatic children.

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# ACRODYNIA: A NEW TREATMENT WITH BAL

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ON MAY 2, 1947, a baby girl, B. K., aged 6 months, was brought to my office with complaints of severe abdominal cramps, marked photophobia, and extreme restlessness. Her weight was normal for her age and her general condition was good. Positive physical findings were red eyes, both conjunctivae and skin around the eyes, her hands, and feet were a bright pink color and very cold to touch. The photophobia was intense and she buried her head in her mother's arms continuously. A tentative diagnosis of acrodynia was made.

In discussing the case with my former associate, Dr. Joseph Patterson, he stated that Dr. Josef Warkany of the Children's Hospital of Cincinnati thought the disease was a mercury poisoning.[1] I discussed the matter with Dr. Warkany over long distance telephone and he told me that he and an associate, Hubbard, had found mercury in varying amounts in the urines of five patients with clinical acrodynia and none was found in the urines of seventeen controls by the same method.[2]

On further questioning, the mother stated that the baby had been given calomel and rhubarb, twelve doses, by the family physician some weeks previously. She was requested to take a specimen of urine to Dr. George Lewis of the Department of Biochemistry of Emory University for analysis for mercury. In talking over the case with Dr. Lewis, he told me that the Department of Medicine of Emory had used a new drug, British Anti-Lewisite, in several cases of heavy metal poisoning and referred me to Dr. Paul Beeson, head of the Department. Over the telephone Dr. Beeson suggested the rationale of using the drug in acrodynia was sound if mercury was found in the urine of our patient, and he referred me to Dr. David James, his resident, for details of therapy.

On May 17, the biochemistry laboratory at Emory reported the presence of mercury in a concentration of 100 gamma per cent in the urine of the patient. Mercury was determined by the method of Long and Nelson (Sandell, E. B.: Colorimetric Determination of Traces of Metals, New York, 1944, p. 324). This involves digestion with hot, concentrated, sulfuric and nitric acids, extraction of mercury and copper with dithiozone in acid solution, and separation of the mercury and copper by extraction with an acid potassium bromide solution into which the mercury dithiozonate passes quantitatively. This method is somewhat laborious and the spread of readings on the Klett photoelectric colorimeter is not very great for amounts of mercury of the order of 15 to 30 gamma. However, the method is stated to be quite specific, and in our hands

From the Departments of Pediatrics and Biochemistry of Emory University.
Presented at a meeting of the Fulton County Medical Society, Nov. 8, 1947.

gave reproducible figures for amounts of mercury of the order of those mentioned above. Blank determinations were run with each set of urine samples.

On May 19, the patient was hospitalized in Crawford Long Hospital and treatment begun with BAL.

### AMERICAN MEDICAL ASSOCIATION COUNCIL REPORT ON BAL[3]

"Arsenic and mercury combine with and block the function of physiologically essential groupings in the cell, specifically the cellular –SH groups. BAL, by virtue of being a ditiol, competes with these cell constituents for the heavy metal and, in the case of arsenic, forms a very stable combination, thus permitting the removal of arsenic from the tissues." Dosage of 5 mg. per kilogram may produce toxic symptoms, dosage of 3 mg. per kilogram rarely does so.

Twenty-five of twenty-six patients with acute mercury poisoning survived following treatment with BAL.

### DETAILS OF TREATMENT

BAL in oil, 10 per cent solution, was given deep into the muscles of the buttocks, preceeded by ½ c.c. of 2 per cent novocaine in the same syringe. Dosage was 3 mg. per kilogram of body weight every four hours for forty-eight hours, then every six hours for twenty-four hours, then every twelve hours for seven days. The injections did not seem to be particularly painful.

By the end of the fourth day of treatment the skin of the hands seemed less pink and warmer and by the sixth day the photophobia was definitely less.

On May 28, the laboratory reported 60 gamma per cent of mercury in the urine (a reduction of 40 gamma per cent).

On May 30, the hands and feet appeared normal in color but some redness persisted around the eyes.

On June 6, the only symptoms persisting were eyes full of tears and slight photophobia.

On June 8, nineteen days from beginning of treatment, the urine was reported free of mercury by Dr. Lewis. As controls, two other children of the same family submitted specimens of urine which were free of mercury.

On June 13, some photophobia persisted, hands and feet were normal, the baby cried a lot and seemed to have some abdominal pain.

On June 20, she was referred, because of persistent photophobia, to Dr. Zack Jackson, an oculist, who prescribed one-half per cent atropine for the iritis, which cleared in three days.

### COMMENT

The observations of Warkany and his associate suggested the inquiry into calomel therapy as a possible etiologic agent in this case. The finding of appreciable amounts of mercury in the urine suggested confirmation. Therapy with BAL seemed logical in view of the reports of the council and the results in mercury and arsenic poisoning obtained at Grady Hospital.

Reduction in the amount of mercury in the urine after nine days of treatment along with subsiding clinical findings was encouraging. Complete disappearance of the mercury in the urine after nineteen days with clearing of all clinical findings except photophobia was encouraging, particularly in comparison with Warkany's[4] cases. All of his cases (five) were untreated. In three children the urine was tested repeatedly. In one case the mercury disappeared within two months. In a second case the mercury was still present after two months, and in a third case mercury could still be found after four months.

It is hoped that publication of this report will stimulate checks on the value of BAL in acrodynia in a large enough series of cases to give it a true evaluation.

We are grateful to Lillian Winship and Victoria Alexander for technical assistance.

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## ADDENDUM

This case was reported at the meeting of the Southern Pediatric Seminar at Saluda, N. C., on July 14, 1947. At that time there were three cases of acrodynia in Dr. Lesesne Smith's Hospital in Saluda. After the above report, two patients were put on BAL therapy as outlined, and the resident physician, Dr. F. E. Elmore, reported to me on July 29, twelve days after beginning treatment, that both patients were clinically free of symptoms of acrodynia. These cases will be reported at a later date.

# ADJUSTMENT OF PARENTS TO CHILDREN IN THE HOME

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## INTRODUCTION

THE psychological reactions which manifest themselves in the adjustment of parents to children are infinite. Not only subtle variations may be observed in one home as compared to another, but different patterns of behavior also may be observed within the psychological structure of the same home, at one time in comparison with another. The numerous factors entering into interpersonal relationships within the family are literally without bound, and, for the most part, beyond the awareness of the participants who make up the home. The reaction patterns of parents to children in the family setting are dependent in great measure upon the total life experiences of these parents, that is, all that has been experienced emotionally in the past, and that which they experience in the present. This discussion is confined to an evaluation of a number of these psychological patterns, which operate in an adjustment between those who are chronologically older and those who are chronologically younger in the home. It does not aim to give direction to or set standards in accord with fixed ideas concerning a more favorable facilitation of such an adjustment.

The family is the basic psychological unit in our society, and has been compared to the mother cell in the social order and cultural structure in which we live. The manner in which psychological forces exert their influence upon each member of the household will influence and modify the psychological responses of others within the family. Any emotional experience which disturbs the psychic equilibrium of one person in the home, whether that person is an adult or a child, will bring about a disturbance in the psychic equilibrium of all the other members of the home. The psychic potentials of the emotional atmosphere of the home are in a continuous state of flux, requiring constant adjustment on the part of all the persons involved. Children make changing demands upon parents to meet their individual needs in the process of their growth and development. They will also bring additional pressure to bear upon, and cause the discomfort of parents who do not provide a stable background for this maturation process. On the other hand, parents demand that children should conform to the standards of the home and fulfill their expectations in order to satisfy their wishes and maintain the structure of the home. There results a continuous delicate interplay of psychological forces to bring about a relative state of well-being in the parent-child relationships.

In the study of psychological problems, there was that initial period in which an attempt was made to understand human behavior by the impossible separation of the psyche and the soma, with the former relegated to philosophical and theological deliberation, and the later assigned to the area of materialistic

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medicine, devoid of psychological consideration. In the recent past this schism in thinking was partially bridged and social taboos were overcome by scientific facts, with the recognition that mental processes and body structure were insolubly bound. But all psychological processes cannot be accounted for on the basis of individual reactions to body needs alone, for we are created by, live with, and are influenced by other human beings, and we create other human beings. This impact of man on man, this constant exchange of emotional stimuli as a most important part of the total body response, has been designated by the term "interpersonal relationships." In the mold of the family structure, such emotional reactions are observed in their greatest intensity, but during the process of socialization there is the extension of emotional experiences outside the home, which in turn directly affects the emotional state within the home. Such a formulation may be applied in the broadest sense, for more and more it is realized that major shifts in interpersonal relationships in this one world of different cultures can, for better or worse, influence the interpersonal relationships in our smaller world within the family. So it is that cultural and family relationships, as well as the personal characteristics of the individual himself, enter into, in varying degree, what happens in the family unit between parents and children who go to make up the nidus of human relationships.

## INFLUENCE OF CULTURE ON FAMILY RELATIONSHIPS

The subtle mode of action in which cultural forces influence family life operates with powerful, interminable effect. Culture is man-made. It shows variations in its organization in a single group at different levels in its structure, and at one period in contrast with another period. In our culture there are organized ways of dealing with the processes of birth, growth, and development, maturity, decline, and death, in which pressures are brought to bear upon adults who, in turn, influence the child's growth and direction in this cycle. The child is not entirely plastic and will bring pressure to bear upon adults, in order to attain needs and derive satisfactions essential to the child's developmental process. The basic needs are phylogenetically determined, but find sources of gratification through many factors operating in a setting of a large variety of external conditions. Variations in social structure will change some needs or create new ones. However, these are secondary to, or modifications of the basic needs which must be satisfied. This was in evidence during the catastrophic upheaval of the social order during this past war, in which deviations from the commonly accepted standards of family structure were condoned, without any marked social concern at the time. In many instances both parents shunned home responsibilities to work, withdrawing in their responsibility toward their children. Adolescents as one group fared poorly, and found temptation an alluring substitute in the face of the disintegrated family structure. Responsibilities were placed upon them which they were not prepared to handle. The disorganized process of emancipation from the home concomitant with the changes of puberty, which at best causes some measure of rebellion, as well as an unstable social order, contributed in part to the dilemma of the rise of juvenile delinquency.

Two factors are worthy of consideration as to cultural pressures brought to bear on relationships within the family. One is the encouragement of the greatest amount of individual freedom and responsibility compatible with the maintenance of the social structure. The other is the cultivation of sexual disciplines characterized by a system of prohibitions, direct or implied. These are, in measure, paradoxical, since on the one hand the development of emotional maturity in the adult is stressed, and on the other there may be the creation of fears and distortions, which may interfere with maturation. As to the sexual disciplines, the cultural taboos related thereto are based not on logic, but on intuitive awareness of the intrinsic dangers inherent in sexual activities other than heterosexual in the marital state. The response of parents to this has been culturally conditioned so that, for example, if a child masturbates at the age of 5, it may evoke a punitive anxiety-ridden attitude on the part of the parents, although the response is quite natural for the child. The social structure permits the family no other recourse but to suppress any overt feelings of gratifications related to the genitals except on maturing and in the monogamous state of marriage. Parents often show anxiety related to the child's curiosity, in their attempt to defer the access of knowledge which the child could handle, compatible with his age and ability to understand. Suddenly, intuitive insight is supposed to be possessed by children when they become adults, ready for parenthood without emotional and intellectual preparation. Whereas our culture demands that there shall be freedom for growth and development compatible with the full potentialities of the individual to assume responsibility, in the area of the sexual disciplines responsibility is thwarted.

Laws and customs recognize the importance of individual freedom. They also recognize the helplessness and the dependency needs of children. Dependency is biologically determined, and the satisfactions of dependency needs are necessary for survival. Parents must, of course, help, protect, and provide the child the opportunity to test, clarify, and sustain himself, in relation to reality. However, this dependency is expected to lessen, the closer the child is to becoming an adult in the maturation process. The parent should encourage individual expression compatible with the child's ability to assume responsibility. It may be observed that where a parent overprotects a child in its developmental process, the child in turn expects all others to satisfy the child's dependency needs. Then it is that social pressure may be brought to bear upon the home, to effect the change in this relationship. Society exerts pressure on all within the home to conform to those principles which maintain the integrity of the social order. These principles vary from one social order to another, but have in common the objective of meeting individual psychobiological needs as related to the group, and these principles are the product of man's creation.

The enforcement of discipline is also influenced by forces external to the home. Discipline, both directional and restrictive, is basically a parental responsibility, and is an educational tool of the adult to encourage the development of the child in the process of growth. Where the parent lacks the capacity to give this direction to the child's growth compatible with the child's ability, and pursues a course of discipline which is excessive or lax, problems of family and

social adaptation occur. Society is concerned with this problem and the social order is very instrumental in molding this and other reactions of parents to children. The parents respond in order to evade social censorship and maintain the social structure.

### INFLUENCE OF FAMILY STRUCTURE ON PARENT-CHILD RELATIONSHIPS

The family constellation within the broader framework of the social order possesses a uniqueness not so strongly in evidence outside the home. The interplay of emotional potentials in all areas of family relationships shows greater force and intensity than is observed out of the home. The struggle to gratify individual needs and satisfactions in the family organization provides the background of parent-child relationships. Even under the most favorable of circumstances, some degree of disturbance is inherent in these relationships in the home. Adults must place very real limitations upon children who at some time or other make demands which, if complied with, would jeopardize the structure of the home. In addition to this, parents who have not been able to integrate their needs and satisfactions on the basis of realism as adults, and instead follow patterns based on past neurotic frames of reference, will find it difficult, if not impossible, to give to the child that which the child requires and demands. It is to be expected, therefore, even in the most ideal household, that intense, uncontrolled, transitory emotional reactions will break forth. Variations are of degree from the better adjusted to the less well adjusted. It can be predicted that, in so far as the parent has not emancipated himself from the past distorted patterns of behavior, so he will adversely influence and be influenced by the child in the present. The child at some time or other provides the framework for the reconstruction of those past patterns of experience not mastered adequately by the adult, and operating in the nonawareness of the present. This adult behavior may be traced back to the inadequate integration of infantile and childhood needs in adjusting to interpersonal relationships. However, other forces also operate, such as the unique characteristics belonging to the specific child and the social and cultural impressions made upon and influencing adult behavior.

All members of the family group present a constant interplay of emotional reactions brought forth in varying degree by the following: competition and rivalry, struggle to satisfy dependency needs, maintenance of prestige values, reaction to discipline, and participation to obtain adequate subsistence and gratification. The parents in this setting play a most important role, for they provide the children with the medium in which the children pass through various stages in the process of development toward ultimate social independence. The experiences derived from the home occur as basic life experiences which, if adequately mastered by the child and parent, provide the framework for adequate cultural adjustment. A parent may find it difficult to assume such a responsibility. Although the adjustment of the parent may appear to be on a reality basis, the relationship to the child creates a medium in which the parent may attempt to relive and master his own childhood experiences. Parents often say they relive their lives through their children rather than they enjoy their

children in their own right as human beings, with distinctive qualities of their own. Some parents find it difficult to yield their children to growth away from them, and cling to them. They desperately hold on to their children to satisfy their own personal needs.

The psychobiologic characteristics of the child and parent in the home limit the field in which interpsychic relationships occur. Individual differences, and the needs and satisfactions at different periods in the life-span of each one, are in a constant state of change. Adjustment within the home is a continuous process to bring about a relative state of the emotional equilibrium. The basic needs must be satisfied in order to maintain the integrity of each member of the family. When these requirements are adequately met, there occurs a proper adaptation without disturbing, anxiety-producing situations. It is biologically determined that the child will endeavor to develop adequate techniques for life eventually independent from parents. The techniques used are commensurate with the child's ability and are dependent upon the biosocial setting in which the child is raised, primarily the home. Parents are important molders of these techniques. The use of aggression on the part of the child is one such technique which parents must meet. This aggression stems from several sources. It may occur intrinsically and spontaneously as one of the primary needs of the child. Some parents find it difficult to handle this aggression and would rather suppress it totally. Another form which aggression takes is that directed toward obtaining other primary needs and satisfactions. However, the most difficult type of aggression is that created by environmental prohibitions to needs which are not adequately met. Often it is directed at grownups in the home, and is displayed as the result of frustration of a gratification, or to ward off a seductive or tempting experience. With this there may be observed an attempt by the child to punish or destroy the disturbing person, or to displace this feeling onto others, or to punish one's self.

Parents also have needs but in a different frame of reference. The family structure provides these needs within cultural specifications, with variations in the subgrouping of a single culture. One of the functions of the maturation process in our society is having children. This implies a capacity to assume responsibility toward the offspring during his growth process. As already mentioned, if maturation of the adult is warped by past emotional experiences, the child will put stress on the parent to help the child meet his needs at the point in his life cycle where the parent could not meet his own needs. And this will set forth in the parent anxiety and defenses to control this anxiety. Such a response on the part of the parent will react to the detriment of the child, as the parent attempts to handle the child's demands. This was observed in a child of 6 who had no constructive limitations put upon his aggressive activity, and as a result showed disorganized aggression. It was not until he entered grammar school that pressure was put to bear on the parent because of the child's intolerable behavior. This parent in turn found it impossible to place constructive limitations on the child's activity. It caused in her resentment, and reminded her of her own rebellion against those who put limitations upon

her activity when she was growing up. Now that she had to place limitations upon her son's activity, she felt helpless to function in a role she resented in others. To be, as she felt, somewhat like those she had defied, was difficult.

### PARENTS' ROLE IN PARENT-CHILD RELATIONSHIPS

That which determines the parent-child relationship to begin with is dependent upon that which each parent brings into the marriage, in the way of relationship of each to the other. Where marriage is motivated by the neurotic needs of one or both parents, or by cultural pressures such as the attitude toward illegitimate pregnancy, children in the home will place additional stress upon the structure of the marriage. The reason for having a child and the circumstances under which a child is conceived may have a great deal to do with the parent-child relationship. Where there is a lack of gratification of neurotic needs sought through marriage, resentment may be directed toward the child as well as toward the marital partner. Or the presence of a child as a symbol of a marriage neither parent wanted, may bring upon the child the unjustifiable wrath of either parent. All too often the child may be used as the battleground of the neuroses of parents. This was observed in a parent unable to accept the integration of the heterosexual function in the marital relationship. A wife attempted to keep her spouse at a distance by bringing the child into bed with her. The child, in turn, exhibited great anxiety, for the child was overwhelmed by responsibility he was not equipped to assume. The father's resentment of the child and the mother's overprotectiveness of the child upon whom neurotic feelings had been displaced, created a dilemma for the child and denied the real source of the emotional difficulties between the parents.

Where two people enter into marriage, each hoping to have his own dependency needs gratified, one desiring to obtain from the other an insatiable amount of affection, tenderness and care, they may be able to sustain each other until a child is born. It is possible then that one or the other parent may look upon the child as a rival for affectional needs and bitterly resent the entrance of the child into the family structure. This intense need of a parent to be accepted and to be cared for may be so great that the parent will not be able to provide the child with the parental love, tenderness, and encouragement a child requires in growth. Instead, for example, the parent may treat the child as the parent treated a sibling of his during his own childhood, or as he treated his father, who appeared to be his rival during his childhood.

Doubt as to the paternity of the child may prove an overwhelming obstacle in the parent-child relationship, with feelings of guilt on the part of the mother and resentment on the part of the father. The child, struggling to be accepted, may make demands on the parents which only intensify their rejection of the child. Whatever is done for the child may be done begrudgingly and this is intuitively sensed by the child. In general, a child knows when he is not wanted. A child born as the result of an unwanted pregnancy for whatever reason may be either rejected or overprotected by parents. The resentment caused by the intrusion of an unwanted member into the household will have a profound and deleterious effect upon the parent-child relationship.

Broken homes caused by divorce, desertion, or death, intensify the basic relationship of the remaining parent toward the children in the home. Such a parent may respond with neurotic benevolence, or overt, hostile reactions directed at the children. This parent is burdened with the responsibility of a dual parental function, which at best is difficult to fulfill. Resentment at being left to care for the children, anger at the fate to which the parent has been subjected, and guilt over realistically or unrealistically contributing to the dissolution of the home, may provoke great anxiety in the remaining parent, as well as a feeling of helplessness and loneliness. One such parent divided her husband's belongings among her children to prove her devotion and love to them. She wanted to obtain their loyalty and to deny the validity of her own role in the separation. In another instance there was a widower who entered into a hasty marriage, so that the responsibility of the care of the children could be shared by the stepmother. She, in turn, wanted to possess the father, and showed bitterness over his loyalty to his children. The stepmother, wishing to be cared for by a parent surrogate, constantly found it impossible to love the children of another woman. On another occasion there was a mother who, each time she looked at her son, literally banged him around, because he reminded her of her former husband who was irresponsible and had deserted the home. In part, she tried to get from the child that which she could not obtain from her husband, often telling the child that he was the man of the house. The boy was bewildered by the emotional pressures the mother applied to him and reacted with hypochondriacal complaints centered about his fear of the mother and his feeling that he was not wanted by anyone. The dissolution of a home is badly tolerated at best by all the family. Relationships in the home necessary for constructive integration of emotional experiences are destroyed or modified, with badly tolerated emotional reactions thwarting healthy personality development in the child.

Other relatives within the home create further problems with which parents and children must cope. A parent operating in frames of reference conditioned by unresolved emotional difficulties related to other relatives within the home may feel helpless to assume responsibility in caring for a child. A child cannot tolerate divided loyalties in the home and needs a stable, consistent background in which parents lend support to the child in his attempts to adjust to the demands of reality. The presence of a grandparent in the home who indulges in bribery and benevolent interest in the child may cause the child much confusion as to his responsibility in the home and what is expected of him. The child may play one relative against the other. Or, the grandparent may try to perpetuate the parent role with the grandchild, thereby creating resentment in the parent. Conflicting sources of authority will cause confusion in the child. Also, other relatives such as brothers and sisters of parents may create past patterns of emotional conflict and may use the child as a way of working out past emotional difficulties in relationship to the parent. One such aunt constantly criticized the child as a means of neurotic retaliation against the parent who was a favorite in the home during their childhood. Even the presence of in-laws in the home for a prolonged period of time may indirectly

affect the emotional equilibrium of the family. This may be observed if one parent finds it difficult to share love relationships which the other parents shows toward the visiting relative. Children intuitively are able to sense the emotional tension caused by the withdrawal of one parent from family participation until the in-laws leave.

### THE CHILD'S CONTRIBUTION TO PARENT-CHILD RELATIONSHIPS

What the child brings into the home because of the child's own characteristics also contributes to and influences the parent-child relationship. Just the sex of the child may profoundly influence the attitude of either parent toward the child. A mother who is unable to accept her own femininity for various reasons based on her past life experiences, and who has little regard for herself as a woman and as a mother, may create in a girl child the monstrosity of trying to be something other than she was intended to be, that is a boy child. Such a child in her unhappy attempt to fulfill this parent's desire will, of necessity, fail. The struggle which results between the parents and the child may cause the child to face insurmountable difficulties, both within and without the home. Also, either parent may show greater affection for a child of one sex as compared to a child of another sex, destroying the self-esteem of the latter child and causing the child to struggle through devious ways to maintain his integrity as an individual. Such a child may respond with aggressive protest in the form of sibling rivalry or rebellious behavior directed at the parents.

Just the intrinsic motor activity of a child at birth may create a state of helplessness on the part of the parent toward the child, especially with the first child because of the lack of knowledge and skill of the parents as parents. Often they will say they had less difficulty carrying subsequent children through infancy, than they had with the first child. The aggressive display of emotion on the part of the infant may create anxiety in the mother, and such anxiety in the mother is quickly transmitted to the child, thereby further increasing motor activity. It has been observed that the motor activity pattern of the child has a variable effect upon a parent, dependent on the parent's own personality development. A quiet child may give the parent an unfounded feeling of security as to the well-being of the child. Within limits, the activity pattern of the child can be modified, but the most important factor in causing such a modification is the parents' emotional relation to each other and to the child. A mother complaining of hyperactivity and disobedience in a 9-year-old daughter noted that from birth, the child was more active than her other two daughters. Activity implied demands made on the mother, which caused the mother much emotional discomfort, for she could not give of herself when she felt constantly deprived emotionally in relation to, and resentful of, her own mother.

The age of a child also enters into the relationship of the parents toward the child. Often parents express their preference for a child at a certain age period of development. A mother would like to keep her daughter in the doll era of 2 or 3 years. Such a parent may be disturbed by the oral demands of the infant, and lives for the day when the infant is able to handle his oral needs

more by himself. The eliminative function of a child may cause an obsessive mother much anxiety until the child has been trained to sphincter control. Sexual curiosity of the juvenile may create much concern in the parent. And puberty with its concomitant struggle for adolescent emancipation and the integration of biologic changes causes many parents extreme discomfort. Such adolescent experiences remobilize past anxieties of parents in their attempt to master unsuccessfully their own forbidden impulses. In general, the transition of the child from one period of growth to the next profoundly influences the reaction of each parent toward the child. The type of reaction of the parent is dependent upon the parent's attempt to live out remnants of his own unresolved experiences which, laden with anxiety, have never been integrated into the adult personality in mature, realistic terms.

The innate intellectual capacity of one child in contrast to another may disturb parents who have been conditioned by false values as to scholastic success. Such a parent may have marked difficulty in adjusting to or accepting a child who possesses mental capacities not in keeping with the parent's aspirations. Even a child with average intellectual endowment may resent the pressures brought to bear by parents with superior endowment. When school comes to be a source of much unhappiness, the child may seek asocial forms of rebellion which disturb the parents. Often such parents resort to punitive measures including physical force, to compel the child to be successful scholastically. Such a parent often is ignorant of the limited potentialities of the child, or the significance of the lag in development of the youngster. This parent also struggles in relation to past experiences which caused much neurotic anxiety, or real anxiety. The value of the clinical psychologist in the area of education has not been fully capitalized upon by educators and by parents. There was observed a parent who worked for wealthy families, although he was limited in his basic intellectual endowment. He pushed his youngster to attain scholastic success in spite of the fact that this adolescent was of borderline intelligence. Teachers appreciated the father's sincerity and also tried to give to this boy scholastic training beyond his capacity to master it. The youth became rebellious toward society and showed delinquent behavior. It was brought out that the father's own childhood insecurity, especially in the area of education, influenced his attitude toward his son. The father also identified with those for whom he worked and hoped that through his son, his feelings of inadequacy and intellectual frustration could be satisfied by a greater knowledge. However, the child's rebellious reaction was in response to an intolerable situation created by a parent, who, of course, was sincere as to his good intentions.

The physical appearance of a child or the health of a child also will contribute to the parent-child relationship. A child may be born with certain physical attributes, real or in phantasy, so that the parent may unconsciously identify the child with himself or with another member of the family, including in-laws. The child then may become the target of nonlogical frames of reference. Whatever the child may do may be met with anticipatory failure or destructive criticism on the part of the parent. Also, where a child suffers from frequent

illness, a parent may cause emotional intensification of the illness and even a prolongation of it. A resentment a parent may have toward frequent or prolonged illness in a child may find expression in devious psychological ways which only intensify the medical problem. Aside from this, illness in a child may create extreme emotional discomfort in the parent based upon the parent's past frustrations in relation to illness. This was noted in a parent who during her childhood required the constant approval of her mother, a very critical woman whom this parent feared. In order to remain in the mother's good graces, this parent during childhood took on tremendous responsibilities for the care of other siblings. One sibling developed infantile paralysis while she was taking care of him and another had frequent attacks of syncope, supposedly due to rheumatic heart disease. This parent developed distortions of reality, feeling that she was responsible for the illness because her mother was away from the home at the time. Her resentment toward these siblings, her fear that some of her fantasies may become real, her feelings of guilt, and her need to punish herself because of these, caused her great discomfort. Now this distortion of reality continued into adulthood so that each time her child became ill, the parent made neurotic demands upon her husband and upon the doctors, to take care of the child so that she would be relieved of any responsibility if anything ominous happened to the child. Several doctors showed little sympathy toward the mother's demands and her husband also resented the child's illness, since he felt that his emotional needs were completely neglected. The illness of this child intensified the already disorganized interpersonal relationships in the home.

The ordinal position of the child in the family also adds to the problems of the parent-child adjustment. No two children have identical experiences in the household, in spite of the false belief that parents treat all children in the home exactly alike. The need to maintain a favorable position in the household motivates a child's demand for affection beyond that which the parents feel is justified. As an example, even when a parent prepares a child for the birth of a sibling in the home, the older child may show such strong resentment toward the sharing of affection as to express hostile feelings toward the young child, and a feeling that the parents have failed him in giving him that which he wants in the way of affection. Such a child seeking affection commensurate with his past needs may provoke parental resentment from those who cannot appreciate this need of the child, or help the child with it. Such a parent feels that merely the announcement of the arrival of a new-born infant should satisfy the child, and no further demands should be made upon the parent.

### CONDITION

In general, the basic reactions of the child will contribute to the relationships within the family structure. Each child in the process of maturation and socialization makes demands upon those he is dependent upon to provide the basis for this development. Children show individual differences and needs which parents must meet. How they are met will determine the relationship of the child to the parent. A child can do neither more nor basically want to do

less than the maturation and organization of his person will permit. If the child's needs are not met adequately, the child will bring pressure to bear on the parent-child relationship. These demands of the child vary with the age of the child as he integrates first one and then another physical, emotional, and intellectual function in his growth process. These functions are related one to another and cannot be separated except for theoretical purposes. It is as important to have knowledge of the emotional and intellectual development of the child as it is to know of the physical process of growth of the child.

There is a constant endeavor on the part of the child to attempt to handle reality in relation to the degree of expansion of the ego of the child. For example, all children at various times resort to fantasy as one means of controlling and adjusting to reality, and all children experience this magic way of controlling and holding intact the child's world. At times, illogical archaic thoughts related to a grownup in the home or to himself, may cause extreme anxiety in the child for fear these thoughts may become real. The adult involved may not be aware of the implication of the child's concern about this, and may contribute to the child's insecurity because of the lack of appreciation of the child's dilemma. The immature ego of the child needs the mature ego of the adult, especially the parent, in order to test out the validity of experiences and rectify illogical, nonrational distortions of reality. Where the reality values of the adult are disturbed, they may have a profound effect on the child's development and cause a disorganization of the child's personality. This, in turn, may materially affect the adjustment of the child in his later years as an adult, and is observable in the epidemiologic transmission of neuroses from one generation to the next.

When parents are able to share responsibilities with equal participation in giving direction to the child's development, based upon respect for and acceptance of the child's capacities, the child will respond with a minimum of anxiety and with a wish to utilize his abilities fully, because of his intrinsic desire to do so. This does not imply identical techniques on the part of parents, but methods appropriate to each parent and accepted by the other, with a unity of purpose in helping the child step by step in the process of development. Family relationships are facilitated where parents do not find the need to resort to gross distortions of reality such as the so-called well-intended lie, as a means of side-stepping responsibility. A child, given the opportunity to relate to father and mother in a truly democratic spirit of individual rights and differences, based upon their proper positions in the household, will be better able thereafter to relate to both men and women, when the child is ready to take his place as an adult in our society. Freedom from illogical distortions of reality, such as false notions passed down in our society from one generation to the next, and fears based on nonreality values, such as neurotic fears, is essential for the development of parents as parents, and children as parents of the future.

The family organization must possess the flexibility to make constant but not too drastic readjustment as this is required by changes both from within and

without the family. Life means the capacity for constant readjustment. Factors which influence this adjustment are related to the innate qualities of the human being and the effect of impact of one human being upon another, in the culture in which they live.

At times, no matter how sound is the advice given parents in relation to problems with their children, the unawareness of and the intensity of the psychological forces motivating the difficulties are so great and so deeply ingrained in the personality structure of the parents and children, that modification can occur only through intensive psychotherapy. This requires a methodological therapeutic procedure based upon a knowledge of the causative factors, and providing the parent and child with a re-evaluation of relationships in accord with reality values.

# Case Reports

## DIABETES INSIPIDUS

### Amelioration Following Tonsillectomy

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FOLLOWING is a report of a case of diabetes insipidus which presented the unusual feature of amelioration of symptoms following tonsillectomy. It was suspected that sphenoid sinusitis was an etiologic factor in the diabetes and that the beneficial results were obtained because of an improvement in the patient's chronic nonsuppurative sinusitis.

R. R., a white schoolboy, aged 7, was first seen on March 5, 1946. His mother reported that he showed a severe thirst with profuse and frequent urination beginning suddenly in January, 1946. She had taken him to the University Hospital, Ann Arbor, Mich., soon after the appearance of symptoms; a tentative diagnosis of diabetes insipidus was made at this time. Between March 5 and 15 he returned to the University Hospital where complete neurologic studies were carried out. They were unable to find any etiologic factor for his diabetes. Skull x-rays were negative. The possibility of hypothalamic tumor was kept in mind, but was considered to have been ruled out. It was found that the patient was allergic to house dust and eggs.

On March 16 he was seen again by me. During the previous twenty-four hours his fluid intake had been 189 oz. (5,760 c.c.) and his urinary output 158 oz. (4,740 c.c.). Specific gravity was not determined, but the urine was reported as colorless.

Physical examination at this time showed obesity of the Fröhlich type, with fat pads over the breasts and girdle and genitalia smaller than normal; the tonsils were large, cryptic, and inflamed, and there was hyperplasia of the lymphoid follicles in the nasopharynx. There was a large amount of purulent material dripping from the posterior nares into the nasopharynx. Nothing else noteworthy was observed.

He was given 5 units of pitressin tannate in oil. The following day his intake was 65 oz. (1,950 c.c.) and his output 42 oz. (1,260 c.c.); the next day his intake was 92 oz. (2,760 c.c.), output 50 oz. (1,500 c.c.). It was observed at this time that there was a noticeable loss of abdominal bloating.

On March 25 it was reported that he had attacks of nausea and vomiting following the injection of pitressin tannate, which had been administered daily. It was therefore decided to give ordinary obstetrical pituitrin. A single daily dose of 1.5 c.c. caused a gastrointestinal response, but no appreciable change in the diabetic symptoms.

On April 1, 1946, he was admitted to the Presbyterian Hospital, Chicago, Ill., on the service of Dr. R. T. Woodyatt. During his hospitalization his urinary volume varied from 2,800 to 4,900 c.c. per day, the lower figure being obtained after a lumbar puncture. The diagnosis at this time was idiopathic diabetes insipidus. His hospital stay was interrupted by a quarantine for measles, and he returned home on April 10.

On Dr. Woodyatt's advice he was given pituitrin in 1 c.c. doses as often as necessary to control his symptoms. It usually took five doses per day to accomplish this, and at times his intake:output would go as high as 1,920:1,200 c.c. The specific gravity of the urine at this time was averaging 1.005.

On May 13, 1946, tonsillectomy and adenoidectomy were performed under ether anesthesia by H. J. Cawthorne, M.D. The patient's course during and immediately following surgery was uneventful.

The day following tonsillectomy it was noticed that it was unnecessary to give pituitrin, and this amelioration of symptoms has persisted. During this next month the intake: output averaged 1,500:1,350 c.c., and the specific gravity of the urine averaged 1.014.

During the period of June 1 to 25, 1947, his urine was examined again at irregular intervals; the intake:output averaged 1,230:960 c.c., and the specific gravity averaged 1.017.

His general health during the last year has been good. He shows a predilection for frequent upper respiratory infections, and he still has a postnasal drip, though not so severely as before tonsillectomy. His mother reports that when he is exposed to cold or to any other situation which might cause nasal congestion he may show an increase in thirst and urination. Use of nasal decongestants or administration of benadryl or pyribenzamine will promptly control the polyuria and polydipsia. Incidentally, neither of these drugs were administered previous to tonsillectomy; it would have been interesting to have observed their effect. It has never been necessary even to consider administration of pituitrin.

## DISCUSSION

According to Jones[1] diabetes is a symptom complex, not an etiologic diagnosis. He has listed the possible etiologies and includes tumor of the pituitary, tumor of the hypothalamus, Hand-Schüller-Christian disease, chronic, encephalitis, syphilis, post-traumatic head injury, pituitary infraction, cerebrovascular accident, subarachnoid hemorrhage, and hypothalamic damage. Kraus[2] quotes Goldzieher as adding chronic inflammation of the posterior lobe of the pituitary and the hypophyseal stalk to this list of etiologies.

In this case it was suspected that the chronic upper respiratory infection included chronic nonsuppurative sinusitis; the sphenoid sinus in particular was thought to be involved. This inflammation, either by direct extension or by causing an edema of this area, resulted in a depression in function of the pituitary gland, especially the posterior lobe. The tendency toward Fröhlich's syndrome could be ascribed to malfunction of the anterior lobe.

It is conceded that there was no objective evidence from laboratory procedures to confirm this hypothesis. But the fact that roentgenograms of the skull were not reported as showing sinusitis does not rule out this condition. X-rays can confirm the existence of sinus pathology only when there is thickening of the lining membrane or when there is pus within the sinus cavity. This point was brought out by Roberts[3] who lists the symptoms of chronic nonsuppurative sinusitis as follows: postnasal mucoid discharge, sensation of nasal stuffiness without actual obstruction, pain in the sinuses without x-ray evidence of suppuration, fatigability, neuritis, and allergic manifestations.

The concept of sphenoid sinusitis causing pituitary dysfunction is strengthened by the case reported by Yaskin and associates.[4] In their patient (who came to autopsy) there was purulent frontal and sphenoid sinusitis with necrosis of the sellar walls of the sphenoid bone plus other infections elsewhere. Previous to death the patient had severe diabetes insipidus, which was ascribed to the inflammatory lesion in the hypothalamic region.

The prompt and dramatic cessation of symptoms following tonsillectomy and the threats of exacerbation whenever congestion of the upper respiratory passages supervenes seemingly indicate a causal relationship between the pituitary dysfunction and the nasopharyngeal pathology.

May we therefore suggest an addition to the list of etiologies of diabetes insipidus: Chronic upper respiratory infection with sphenoid sinusitis?

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# SEPTICEMIA DUE TO ESCHERICHIA COLI

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SEPSIS due to *Escherichia coli* is seen most frequently in infants, but fortunately it is not common. The prognosis prior to the advent of chemotherapeutic and antibiotic agents was poor. Although it has improved with these agents, the prognosis still is not good. In 1941, Herrell and Brown[1] reported a recovery rate of 78.6 per cent in fourteen adults treated with sulfonamides as contrasted to a rate of 61.9 per cent in twenty-one adults treated without sulfonamides. Kanof and associates[2] treated eight children with sulfonamides, and 62.5 per cent recovered.

Reports on the efficacy of streptomycin in the treatment of *Esch. coli* septicemia are accumulating. Keefer[3] collected a series of thirty-four cases of subjects treated with streptomycin, with 73 per cent recovering. Nichols and Herrell[4] reported six patients treated with streptomycin with five recoveries and one death due to acute vegetative endocarditis. The average daily adult dose was 2 to 3 Gm., but no details of the cases or of the treatment are included in these reports. Alexander[5] reported the recovery of a 19-year-old soldier who was acutely and gravely ill with *Esch. coli* septicemia and meningitis, the source of infection being an osteomyelitis of the tibia following a war wound. Shields[6] reported the case of a critically ill 5-week-old infant with *Esch. coli* bacteremia and meningitis who was treated with 30,000 units of streptomycin intramuscularly every three hours (32,000 units per pound per day), plus 30,000 units intrathecally daily for ten days. Complete recovery without sequelae ensued.

## CASE REPORTS

At the North Carolina Baptist Hospital, two infants with *Esch. coli* septicemia have been seen recently. One of the infants died a few hours after admission before therapy could be instituted, and diagnosis was made by antemortem blood culture. The second infant did not improve on sulfadiazine therapy, but recovered promptly on streptomycin therapy. These cases serve to emphasize the seriousness of *Esch. coli* septicemia and the success of treatment with streptomycin against a sulfonamide resistant strain of *Esch. coli*.

Case 1.—A 5-day-old female was admitted Dec. 16, 1946, because of cyanosis and blood oozing from the rectum. The pregnancy and labor were uncomplicated. The infant weighed 6 pounds at birth and had been ill since the second day of life. She nursed poorly, regurgitated several times, and seemed to have lost considerable weight. She became cyanotic and required artificial respiration. Intermittent cyanosis continued until admission. There was a small spot of blood on the diaper daily. She seemed feverish each of the three days before admission.

*Physical Examination.*—Temperature, 101.4° F.; pulse, 160; respirations, 80; weight, 4 pounds, 13 ounces. Examination revealed a small, undernourished, restless, irritable infant who appeared acutely ill. There was mottled cyanosis of the hands, feet, and about the mouth, with large ecchymotic areas on the

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right arm and over the chest. The anterior fontanel was 4 cm. in diameter and of normal tension. There was a small ulcer on the hard palate. The respirations were rapid without retraction of the interspaces. The heart and lungs were normal. The liver was palpable 3 cm. below the right costal margin. The Brudzinski and Kernig signs were absent.

*Accessory Clinical Findings.*—Urine: albumin 3 plus. Microscopic examination showed 1 to 2 granular casts; 2 to 3 white blood cells; no red blood cells; and many epithelial cells per high powered field, centrifuged. Blood: hemoglobin, 21 Gm.; red blood cells, 4.25 million; white blood cells, 6,560 with 2 per cent segmented polymorphonuclears and 2 per cent nonsegmented polymorphonuclears; 84 per cent small lymphocytes; and 12 per cent unclassified cells which were fragmented. The carbon-dioxide combining power was 16.8 milliequivalents. Fluoroscopy of the chest was negative. The stool was positive for occult blood and bile. The Kahn test was negative. The clotting time was 2 minutes, and the bleeding time was 5 minutes. The blood prothrombin time was 37 seconds with a control of 25 seconds. Because it was felt that the infant had an overwhelming infection, she was given 2,000 units of penicillin every three hours and one injection of 64 mg. of sodium sulfadiazine. She was also given vitamin K, plasma, and ⅙ M. sodium lactate intravenously and subcutaneously.

The cyanosis continued in spite of oxygen, and she expired nine hours after admission. Antemortem blood culture had a heavy growth in sixteen hours of *Esch. coli communis*, sucrose negative, indole positive, and methyl red positive. Post-mortem spinal fluid culture also revealed *Esch. coli communis*. Autopsy revealed a diffuse hepatitis and hemorrhagic endocarditis of the mitral and tricuspid valves, but gram-stain studies on these valves failed to show any organisms.

CASE 2.—A 4-month-old female was admitted Dec. 18, 1946. The past history was noncontributory, and the infant had apparently been quite well until twelve hours before admission, when she seemed restless on awakening in the morning and fretted while at the breast. She vomited one time. She continued to be restless, feverish, and increasingly irritable during the day. Review of systems was entirely negative.

*Physical Examination.*—Temperature, 103.4° F.; pulse, 188; respirations, 60; blood pressure, 70/45; weight, 12 pounds. Examination revealed a well-developed, slightly undernourished, extremely irritable 4-month-old female. There was pallor of the skin, but no petechiae. The anterior fontanel was $3 \times 4$ cm. and slightly full, but not tense. The neck was not stiff, but the general irritability made examination difficult. The heart and lungs were normal. The liver was palpable 2 cm. below the right costal margin. There was tenderness in the left upper quadrant, but no rigidity or mass was palpated. No meningeal signs were elicited.

*Accessory Clinical Findings.*—Urine: 3 plus albumin; 15 to 20 white blood cells per high powered field, uncentrifuged with numerous white blood cell clumps. Blood: hemoglobin, 9.5 Gm.; red blood cells, 5.03 million; white blood cells, 13,000, with 40 per cent segmented polymorphonuclears and 7 per cent nonsegmented polymorphonuclears; 1 per cent basophiles; 5 per cent large lymphocytes; 37 per cent small lymphocytes; and 10 per cent monocytes. Kahn was negative. Lumbar puncture showed 6 monocytes; Pandy test was negative; and sugar 40 to 50 mg. per cent. The urine and blood cultures taken on admission were positive for *Esch. coli communior*, sucrose, indole, and methyl red positive.

*Hospital Course.*—The infant was acutely ill, and sulfadiazine was begun on admission. The temperature spiked to 103° and 104° F., and she continued to be very restless and irritable. There was no improvement in her clinical con-

dition. Two days later, the organisms obtained on blood culture were found to be inhibited by a concentration of streptomycin between 16 and 64 units per cubic centimeter, and resistant to 64 mg. per cubic centimeter of sulfadiazine. Streptomycin was begun 120,000 units every three hours (80,000 units per pound per day) at this time. The urine and blood cultures became negative twenty-four hours later and were sterile on all subsequent examinations. There was marked improvement in her general condition, and the temperature dropped steadily to normal in four days.

Although no meningeal signs could be elicited, repeat lumbar puncture on the third day revealed slightly cloudy fluid with 82 polymorphonuclears, 62 monocytes, and 367 red blood cells. The Pandy test showed a trace of globulin, and the sugar was 40 to 50 mg. per cent. The smear of the sediment was positive for gram-negative bacilli. 25,000 units of streptomycin were given intrathecally. The culture of the spinal fluid revealed no growth, and the following day the spinal fluid cell count had dropped to 10 polymorphonuclears; 26 monocytes; and 1,000 red blood cells. The smears and cultures for organisms were negative. No further intrathecal therapy was given.

On the sixth day of therapy the temperature rose to 101° F., and she vomited two feedings. Examination revealed no cause for the fever. It was felt that this might be a reaction to the streptomycin, so the drug was discontinued. The temperature returned to normal, and there was no further vomiting. Otherwise, there were no toxic effects. She was discharged on the thirteenth day, having gained 10 ounces.

Follow-up studies one month after discharge again revealed a pyuria. She was readmitted March 4, 1947, for study. Urine cultures showed colonies of *Esch. coli communior* which were sensitive to 4 units of streptomycin per cubic centimeter and 64 mg. of sulfadiazine per cubic centimeter. The cultures became sterile after retreatment with streptomycin. Intravenous pyelograms showed no gross deformities of the urinary tract.

## SUMMARY

Two cases of bacteremia due to *Esch. coli* are reported: (1) a 5-day-old infant was in extremis on admission and died nine hours later before appropriate therapy could be instituted; (2) a 4-month-old infant with blood stream and urinary tract infection due to *Esch. coli* who recovered after treatment with 80,000 units of streptomycin per pound per day for six days, having shown no clinical or bacteriological response to previous treatment with sulfadiazine for three days. She received a total of 5,850,000 units of streptomycin.

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# CHRONIC LYMPHOID LEUCEMIA IN CHILDREN

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CHRONIC lymphoid leucemia is a disease of adult life characterized by a greatly enlarged spleen, enlarged peripheral lymph nodes, and a hyperleucocytosis in which the majority of the cells are small mature lymphocytes. The disease is a chronic one and usually lasts two to five years. Although occasional cases have been reported in younger adults, none has been found in children. It is stated in at least two of the current pediatric texts[1, 2] that chronic lymphoid leucemia does not occur during childhood. There are, however, certain reports in the literature of patients in whom the diagnosis was made. A careful scrutiny of these suggests that they were more likely examples of acute leucemia, which is usual in childhood. Brief mention of certain of these reports will be made later.

The present report concerns a child with a blood dyscrasia and clinical findings that suggest chronic lymphoid leucemia much more than the acute form. A brief summary of this case follows. S. T., a white girl 3 years of age, was first seen in February, 1947. The history was that at the age of 5 weeks, during a routine health examination, she was found to have a considerably enlarged spleen. Because the splenomegaly persisted, she was admitted at the age of 5 months to St. Mary's Hospital in St. Louis for study. During a period of three weeks there she had a number of blood examinations in which the total leucocytes varied from 31,000 to 62,000. Stained smears showed 70 to 94 per cent of these cells to be small mature lymphocytes. The erythrocytes varied from 4 to 5 million, and the hemoglobin from 10 to 14 Gm. per cent. Platelets numbered 190,000. Smears from a marrow puncture showed that 89 per cent of the cells were oxidase negative, and a high percentage of these cells were lymphocytes.

During the ensuing months there were frequent bouts of nose and throat infection for which the tonsils and adenoids were removed at the age of 2 years. Following this, she continued in good health until the age of 3 years, at which time she developed another upper respiratory infection. Because of persistent anorexia, cough, and malaise, she was brought to our clinic.

Physical examination revealed a well-nourished and well-developed child with signs of an acute upper respiratory infection and nasal obstruction. A large adenoid mass was present. The cervical lymph nodes were slightly enlarged, but there was no enlargement of the axillary or inguinal nodes. The striking physical finding was the enlarged spleen which was very hard and extended to the pelvic brim. The liver was also enlarged three fingerbreadths below the costal margin. There were no skin hemorrhages, and the tourniquet test was negative.

*Clinical and Laboratory Tests.*—The erythrocytes numbered 4,980,000, the leucocytes 77,000, and the platelets 558,000. The hemoglobin value was 9.8 Gm. per cent and the reticulocyte count was 6.8 per cent. Stained blood smears showed 90 per cent of the leucocytes to be small lymphocytes. A careful search showed no immature forms. Bleeding and clotting times were normal. The icterus index was 5, and the fragility of the erythrocytes was normal. Chemical analysis of the blood showed all the elements to be within normal limits. Biopsy of the tibial bone marrow revealed 72 per cent of the cells to be lymphocytes. No "blast" cells were seen, and there was no decrease in erythroid elements or in megakaryocytes. Blood Wassermann and Kahn and the tuberculin skin test were negative. Examination of the urine was negative. Roentgenograms of the skull and right lower extremity showed no bone changes.

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During her hospital stay of two weeks, the respiratory infection cleared with a short course of penicillin therapy, and she was given two small blood transfusions. The leucocytes varied in this time between 32,000 and 95,000 with no essential change in the differential picture. Although her condition remained good, she was given x-ray irradiation on two occasions (a total of 300 roentgenograms).

When she was seen one month later, the leucocytes were reduced to 6,500 with 86 per cent lymphocytes. At this time a large adenoid mass was removed. The spleen was slightly smaller but still reached 1 cm. below the umbilicus.

She was next seen in June, 1947, with the history that she had been in excellent health for a month or so following the adenoidectomy but that in the preceding few weeks she had become progressively more irritable and more easily fatigued. One week prior to entry an increasing pallor was noted, and the child appeared quite ill. An examination of the blood at this time showed an erythrocyte count of 2,030,000 with a hemoglobin of 6.3 Gm. per cent. The leucocytes numbered 34,000 with a differential count of 90 per cent lymphocytes, 9 polymorphonuclears, and 1 stab. There was no thrombocytopenia. Bone marrow smears at this time showed extensive infiltration with small lymphocytes. There was a great reduction in erythrogenic elements, but the megakaryocytes appeared normal in number. Although one or two small cervical lymph nodes were palpable, there was no enlargement of the axillary or inguinal nodes. The spleen was still 1 cm. below the umbilicus. After two transfusions totalling 450 c.c., the hemoglobin was 14 Gm. per cent, and she showed marked clinical improvement. In summary, a 3½-year-old girl had had a very large firm spleen since early infancy and a continued hyperleucocytosis. The peripheral blood and the bone marrow showed a high percentage of small mature lymphocytes. There was no general lymphatic enlargement, thrombocytopenia, or hemorrhage. During the four months of observation, however, a severe anemia developed.

## DISCUSSION

True chronic lymphoid leucemia as seen in adults is characterized not only by a much enlarged spleen and peripheral lymph nodes but by the presence in the blood and bone marrow of large numbers of small lymphocytes. The clinical course is one measured by a few years rather than a few months. It is also characterized by the absence of early thrombocytopenia, hemorrhagic tendencies, and rapidly developing anemia. When such symptoms do appear in chronic lymphoid leucemia, they are usually in the latter stages of the disease and are attributed to an encroachment on blood-forming elements by abnormal hyperplastic lymphoid marrow. In acute leucemia, on the other hand, in addition to the enlarged spleen and lymph nodes, thrombocytopenia, hemorrhages, and severe, rapidly developing anemia are common. The immature cells dominating the blood picture and the marrow in acute leucemia are of an entirely different morphology from the mature lymphocyte. While the duration of acute leucemia is usually only two to four months after the manifestations first appear, it may be considerably longer. Such cases are sometimes referred to as "subacute leucemia" but resemble acute leucemia in all respects except for the prolonged duration. In the records of the St. Louis Children's Hospital there are at least six cases which lasted more than ten months. One of these patients lived twenty months. In most of these children, progress of the disease was slow, but all had anemia and thrombocytopenia with the presence in the peripheral blood of immature leucocytes early in the illness. The diagnosis of chronic leucemia apparently must be made on criteria other than the duration of the leucemic illness alone.

As examples of the published reports of chronic lymphoid leucemia in children, brief summaries of three papers will be given. These were selected from a number of others in which it was felt that the disease described was obviously not chronic lymphoid leucemia.

In 1932, de Bruin[3] collected from the literature ten reported cases of chronic lymphoid leucemia in children and added one of his own. All of these showed profound anemia and hemorrhagic manifestations. The leucocyte counts varied from 750 to 658,000 with 74 to 100 per cent lymphocytes. Unfortunately, morphology of the lymphocytes was not described, nor were platelet counts recorded. The duration of illness in these patients varied from three to eighteen months. The criteria apparently used by the author in calling these chronic rather than acute leucemia were: (1) that the disease was insidious in onset rather than acute, (2) that it lasted more than three months, and (3) that there were no necrotic lesions in the mouth.

A case of chronic lymphoid leucemia in a 12-year-old boy was reported by Vas de Mello.[4] In this child the liver, spleen, and lymph nodes were enlarged, and he had been pale and dyspneic for several months. The leucocytes numbered 77,400, with 85 per cent lymphocytes of undescribed morphology. Anemia was moderately severe. No mention was made of skin hemorrhages, and platelet counts were not recorded. Death occurred four months later.

Blackfan and Diamond[5] reported a case of chronic lymphoid leucemia in an 8-year-old boy who lived for eight and one-half months after the onset of symptoms. When first seen, the boy was not acutely ill but showed considerable enlargement of the liver, spleen, and lymph nodes. The platelets and erythrocytes were within normal limits. The leucocyte count was 30,000. Stained smear showed 35 per cent of these cells to be lymphoblasts. No bone marrow studies were recorded, but a lymph node biopsy showed infiltration of the tissues by immature lymphoid cells. X-ray therapy was given without benefit. Before death he showed a typical picture of acute leucemia with anemia, thrombocytopenia, and lymphoblastosis.

In each of these instances evidence appears inadequate for the diagnosis of chronic lymphoid leucemia.

## SUMMARY

Chronic lymphoid leucemia in children was reviewed briefly with the suggestion that the cases reported were probably acute leucemia with a somewhat longer course than usual. Detailed observations were given on a 3½-year-old girl who had had a very large, firm spleen since early infancy and who had a persisting hyperleucocytosis, the majority of the cells being small mature lymphocytes. There was no thrombocytopenia or hemorrhagic diatheses. The bone marrow showed a marked lymphocytic infiltration. In spite of the fact that there was no general enlargement of the lymph nodes, it was felt that this child had sufficiently characteristic findings to classify the case as one of chronic lymphoid leucemia.

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# Clinical Conference

## CONFERENCE AT THE CHILDREN'S HOSPITAL OF MICHIGAN

AUGUST, 1947

DR. PAUL V. WOOLLEY, JR., PEDIATRICIAN-IN-CHIEF

### Case 1. Bronchiectasis

DR. JOHN D. BURNETT (Assistant Resident in Pediatrics).—The patient, a 5-year-old boy, first entered the hospital on Oct. 29, 1946, because of hemoptysis of five days' duration. He had been well until the preceding August, when, while on vacation in the northern part of the state, he developed a cough which was followed in a few days by fever and chest pain. A month of therapy with penicillin and sulfadiazine was given before he returned to Detroit, supposedly convalescent from pneumonia and empyema. Two weeks later, or six weeks before admission here, the cough recurred and became productive of blood-streaked sputum, culminating in several episodes of frank hemoptysis. He appeared apathetic, and an area of dullness, over which the breath tones were suppressed, was present at the right base. His temperature was 100° F., and the laboratory data were helpful primarily in a negative sense; the white blood cells were slightly increased, there was no reaction to tuberculin, and the sputum was not purulent but on culture contained a coagulase-positive *Staphylococcus aureus*. Roentgenograms (Figs. 1 to 3) revealed only what might be expected from the physical findings.

During the initial phase of this earlier admission his cough continued troublesome, and a low-grade fever persisted despite penicillin inhalations. Inflammation with dilatation of the lower right bronchus was described on bronchoscopic examination, and films obtained after the instillation of lipiodol demonstrated bronchiectatic changes in the same area. Following this procedure were several episodes of brisk hemorrhage, severe enough to necessitate transfusion, and penicillin inhalations were resumed. Various therapeutic approaches were considered, and a conservative course was decided upon in view of the minimal parenchymal involvement, the age of the patient, and the desire to evaluate more completely penicillin aerosols. He was discharged, therefore, and followed regularly in the clinic. During the next nine months he led an active life, though there were periods when his cough was troublesome and though he reacted to respiratory infections with an exaggerated febrile response. The parents complained that at times his breath was foul, but there was no dyspnea, cyanosis, pain, or hemoptysis. No change was discernible by x-ray, and there was no increase in body weight.

He is now readmitted for evaluation and for consideration of more active therapy. Examination still reveals little other than dullness and diminished breath tones over the right base and daily temperature fluctuations to as high as 100.5° F. Once more the laboratory findings are not remarkable. Dr. Evans has films for comparison with earlier observations.

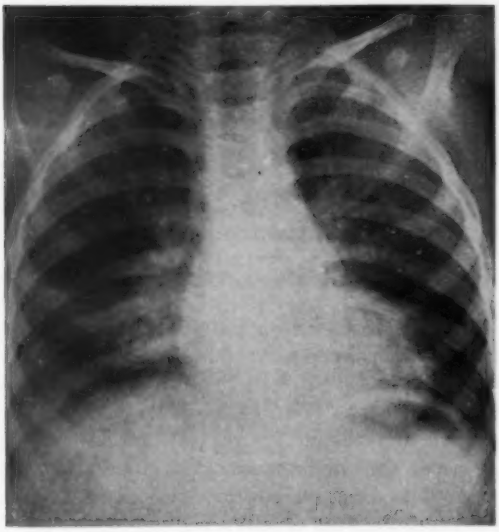

Fig. 1.—Case 1. Initial x-ray showing infiltration of the lower third of the right lung field most marked medially and confined entirely to the lower lobe.

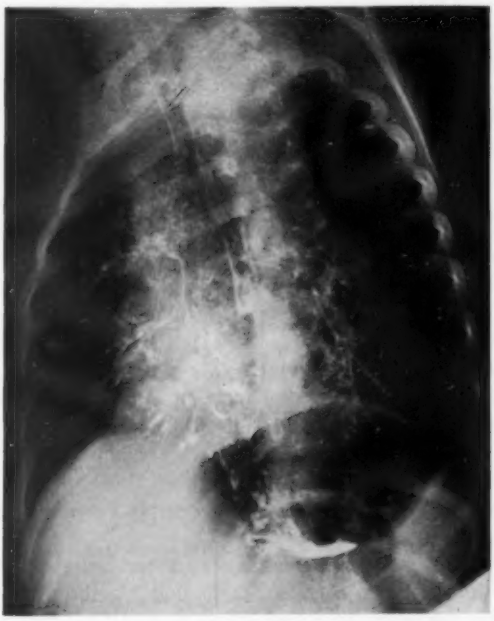

Fig. 2.—Case 1. After instillation of lipiodol, demonstrating the saccular enlargements of the terminal bronchi in the lower, medial, posterior portion.

DR. WILLIAM A. EVANS (Roentgenologist-in-Chief).—Here is the initial film taken Oct. 30, 1946 (Fig. 1), and in it you see an infiltration of the lower third of the right lung field. This is most marked medially and is confined entirely to the lower lobe. There is no pleural reaction and no atelectasis. This film (Fig. 2) was taken Nov. 12, 1946, after the instillation of lipiodol, and demonstrates the saccular enlargements of the terminal bronchi in the lower, medial, posterior portion. Here is what we take to be the interlobar fissure, and from its location we can be safe in saying that the bronchiectatic process is confined entirely to the lower lobe. The final film (Fig. 3), dated Aug. 1, 1947, shows, if anything, an increase in the amount of infiltration as well as an area of what appears to be atelectasis. There is no evidence of extension to the remainder of the right lung or to the left side.

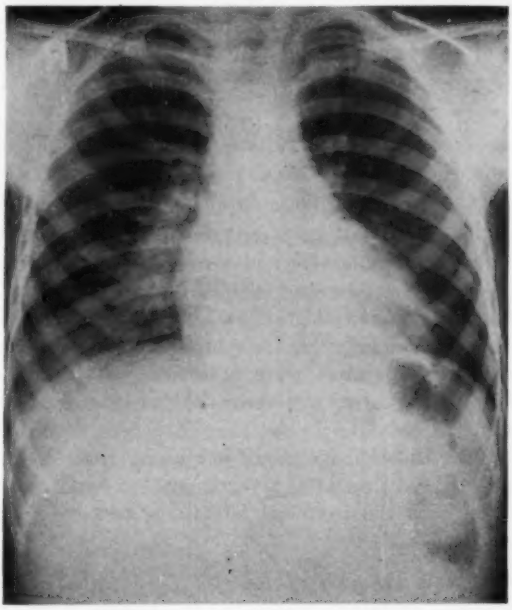

Fig. 3.—Case 1. Final film showing increase in amount of infiltration as well as an area of what appears to be atelectasis. There is no evidence of extension to the remainder of the right lung or to the left side.

DR. PAUL V. WOOLLEY, JR. (Pediatrician-in-Chief).—When this child was presented last fall, discussion centered about three questions. First, what caused the lesion? Second, what is the course and prognosis of bronchiectasis in this age group, and third, what should be done for the patient? Certainly a unilateral and circumscribed bronchiectasis is most frequently due to interstitial pneumonitis or to bronchial obstruction with some degree of atelectasis and peribronchial fibrosis. Since our patient was not in contact with other children at the onset, there were no symptoms in the remainder of the family, August is a poor time for primary respiratory infection, and fever, though present, was

a late development, it was felt that a bronchial obstruction was the better possibility. Little consideration was given to purulent bronchitis because of the sharp delineation of the process and the lack of sputum. Someone suggested a bronchial tumor or hemangioma, and it was felt that this could be ruled out at bronchoscopy. In the presence of a negative reaction to tuberculosis, foreign body comes first to mind as a cause for bronchial obstruction, so that bronchoscopy was undertaken despite the recent hemoptyses. When nothing was found we were forced to conclude that no intrinsic obstruction was present or, at least, if it had been, we were now concerned with an end result.

In regard to the course and prognosis for bronchiectasis in this age group, we have all been impressed by the observations of our neighbors at Maybury who point out that once bronchial continuity is re-established, few children have symptoms even though roentgenoscopic evidence of dilatation remains.[1] This increased caliber of the lumen would thus seem to depend upon surrounding fibrosis rather than destruction of bronchial integrity. With this concept in mind a conservative course was ordered.

Today we are faced with a little different situation. There has been no tendency for improvement either clinically or roentgenoscopically, and we must assume that some of the failure to gain is on the basis of the pulmonary lesion. The possibility of lobectomy has been suggested and Dr. Clifford Benson, our thoracic surgeon, who, unfortunately, is not here today, has been consulted. He believes that serious consideration should be given intervention now since the child is in relatively good condition and there is, so far as we can see, no pleural reaction. We both, however, are completely convinced that a repetition of the bronchoscopy is imperative since a foreign body, better than anything else, would explain this process, and since the persistence of symptoms would suggest that it was still present. It has, therefore, been agreed that Dr. Arthur E. Hammond will have another look and, if nothing is found, a lobectomy will be seriously considered because of the persistence of local change, evidence of systemic retardation, and the technical advantage now over what might exist in another year.

QUESTION.—What is the risk of lobectomy and what are the chances of scoliosis or other complications?

DR. WOOLLEY.—We have discussed this with Dr. Benson, and he is inclined to minimize all deterrents. I personally am amazed, as must be all pediatricians, with the tremendous strides thoracic surgery has made. This requires, however, a complete team with not only experienced operators but also the best in anesthesia as well as pre- and postoperative supervision.

QUESTION.—What role might inflammation higher in the respiratory tract play in keeping the bronchial picture alive?

DR. WOOLLEY.—This has been investigated rather thoroughly since the association of sinusitis and rhinitis with bronchiectasis is well established. Our otorhinolaryngologists have provided a clean bill of health.

FOLLOW-UP OF PATIENT, ONE WEEK LATER

DR. WOOLLEY.—Dr. Weiss has a report to make on our patient from last week.

DR. ARNO W. WEISS (Resident in Otorhinolaryngology).—Bronchoscopy was repeated by Dr. Arthur E. Hammond. Upon entering the right main-stem bronchus a foreign article presented, and I have brought it with me. It is a head of fox-grass measuring 2 inches in length and ¼ inch in diameter. This was removed easily and the patient has had no unfavorable reaction from his experience.

QUESTION.—Do you think this was the source of the whole trouble or is it something that came to lodge in the area after the onset of symptoms?

DR. WOOLLEY.—I am willing to bet that this is the complete story. Recall that the difficulty began in August, that this is late summer grass, and that it now is August a year later; examination of the relic will convince you that it has been present more than a few weeks.

QUESTION.—How does this change our plans for therapy?

DR. WOOLLEY.—Again, I can refer only to the Maybury experience that once the bronchial irritation is relieved bronchiectasis may persist as an anatomical condition but does not necessarily cause clinical symptoms. Certainly all thoughts of surgery will be postponed until an adequate period has passed to allow reappraisal: we will send him home and see him again in three months. In closing this case temporarily I would like to re-emphasize the importance of remaining ever alert to the possibility of foreign body in children with pulmonary complaints. You will recall the excellent presentation of Dr. John Burnett at the residents' program for the staff when he pointed out that the majority of children admitted with foreign bodies in the bronchi had been seen at least once by outside physicians without a correct diagnosis being reached.

ADDENDUM TO CASE 1

A final note can now be attached (December, 1947). Francis is entirely free from symptoms; his physical examination and chest film are essentially negative. As an outgrowth of this presentation, a new history was taken for a 3-year-old girl, who was hospitalized at the time with "pneumonia," and her onset dated to a choking spell experienced while playing in a field. Bronchoscopy revealed nothing, but, since her symptoms persisted, it was repeated Dec. 1, 1947, and the macerated remains of an unidentifiable grass head removed, four months after aspiration.

## Case 2. Polyostotic Fibrous Dysplasia

DR. E. BRYCE ALPERN (Assistant Resident in Pediatrics).—The patient, a Negro girl, 3 years, 3 months old, was admitted because of enlargement of the breasts during the past month and a bloody vaginal discharge of two weeks' duration. Mammary hypertrophy appeared first on the right and two weeks

later on the left, was not painful, and no history of trauma was obtained. The vaginal discharge has been sufficient only to stain her clothes. It has not been purulent, and there has been nothing to suggest a foreign body or injury. The external genitalia have not enlarged, and there has been no headache, anomaly of vision, or symptoms referable to the abdomen. She has been followed in our clinic since birth and has always been well. Growth and development have been timely, and a gain of 4 inches in height and 6 pounds of weight were recorded during the past year, amounts rather in excess of average. The mother, father, and three siblings are in good health.

Fig. 4.—Case 2. Left hand of patient. Note varying degree of involvement in the metacarpals.

Examination showed her to be 41¾ inches tall, to weigh 32 pounds and to be in good nutritional state. Pulse and temperature were as expected, and her blood pressure was 100/60. Ocular movements and fundi were normal. Her breasts showed diffuse hypertrophy, and on the left buttock, as well as behind the left knee, were irregular, deeply pigmented "Mongolian blue spots." Nothing out of the ordinary was felt in the abdomen or pelvis. The external genitalia were unremarkable, and no pubic nor axillary hair was present.

Laboratory data to date include negative urinalysis with good specific gravity, blood cell counts within acceptable range, and negative tuberculin and

Mazzini tests. The blood calcium is 8 mg. per cent; the phosphorus, 8 mg. per cent; the phosphatase, 0.3 Bodansky units; and blood cholesterol, 165 mg. per cent. Some endocrine studies have been obtained through the Harper Hospital facilities including 17-ketosteroids, 1.8 mg. per twenty-four hours; estrogen, 20 gamma per twenty-four hours; no pregnandiol; and less than 7 mouse units of F.S.H. per twenty-four hours. The vaginal epithelium was of the adult type and showed estrogenic effect.

Dr. Evans has complete roentgenoscopic studies.

Fig. 5.—Case 2. Left elbow of patient showing areas of increased density as well as rarefaction.

Dr. William A. Evans.—Films of the skull, chest, and abdomen show nothing enlightening. Those of her skeleton, however, reveal widespread bony changes characterized by both demineralization and overgrowth. Although present in most of the bones, the more marked lesions predominate on the left side of the body while some bones are spared completely. These are characteristic of polyostotic fibrous dysplasia and are difficult to confuse with changes seen in any other condition. The distribution does not resemble that of von Recklinghausen's syndrome, where they tend to be about the knees and never generalized. The character of the individual lesion sets it apart from metastatic tumor rests and from the various lipoid diseases in that it is not punched out and shows both demineralization and deposition of new bone. There is no predilection for epiphyseal zones such as characterizes the various deficiency states of childhood. While changes in the bones of the skull are rather common, we do not demonstrate them in all instances nor look upon them as necessary diagnostic criteria.

Dr. Paul V. Woolley, Jr.—Dr. Alpern has been most interested in this little girl and has been kind enough to review the recent contributions on this condition.

Dr. Alpern.—A syndrome characterized by localized cutaneous pigmentation, fibrous dysplasia of bone, and, in girls, precocious puberty, was described ten years ago by Albright and his associates.[2] Since then a considerable litera-

ture has accumulated on the subject, dealing not only with case reports and attempts to explain the pathologic changes but also with the relationship of these changes to earlier described conditions with which one or more manifestations might be confused.

Difficulty has centered especially around the separation of this syndrome from neurofibromatosis and from the various lipodystrophies or xanthomatoses. Albright[3] has recently considered the differentiating features and has answered rather satisfactorily the arguments of those who deny the individuality of polyostotic fibrous dysplasia.

It is so common to find irregularities in pigmentation among Negro children that in the present case little attention was paid to these during the initial physical examination. After discovery of the bony lesions they were considered more closely, and then it was seen that they are more distinct than are the ordinary "Mongolian spots" and that the edges are irregularly serrated in the typical "coast of Maine" pattern. No cutaneous neurofibromas are present, and this has been emphasized by Albright as one of the best points of differentiation between von Recklinghausen's disease and polyostotic fibrous dysplasia. The endocrinologic observations support those already on record in that estrogen appears to be the only hormonal substance increased. Two explanations have been offered for the precocious puberty of females with this syndrome. The first is a distinct hypothalamic lesion which initiates pituitary activity, and the other is that bony changes in the base of the skull may actually impinge upon the hypothalamus and secondarily cause the release of activators. There seems to be no satisfactory explanation for the absence of precocity in males with this syndrome.

So far as treatment is concerned we have nothing to offer, and in general the state is not incompatible with ordinary existence; in fact, the bone lesions, at least, tend to regress as age increases. X-ray is ineffective against the bone changes, in marked contrast to the finding in most of the xanthomatoses, which are ordinarily quite radiosensitive. The cause of this entity remains unknown although it would appear to be in the nature of a developmental anomaly.

QUESTION.—Why does not this child have pubic hair like most of the "constitutionally" precocious do?

DR. ROBERT BAUER (Chief of the Endocrine Clinic).—If we look upon this girl as similar to the normal pubescent except for her young age and realize her entire symptomatology is only of four weeks' duration, I do not think we need be surprised to find some of the secondary characteristics ahead of others. She probably will develop the rest fairly soon. I think it is worth while once more to point out the value of the hormone titrations since in this instance they separate so clearly the hypothalamic type of puberty from changes due to tumors of the ovary or adrenals.

DR. WOOLLEY.—Before this child is released I believe we should repeat both the phosphorus and phosphatase determinations. I can see no reason for elevation of the former, and ordinarily the latter is increased with such extensive

bone change. To the best of my knowledge parathyroid changes have not been described with Albright's syndrome although hyperthyroidism has been present on several occasions.

### Case 3. Ritter's Disease

Dr. Mary J. Stern (Assistant Resident in Pediatrics).—This 18-day-old baby was transferred here on the second day of life because of an extensive skin disorder which had been present at birth and had increased thereafter. The mother had been well throughout pregnancy, her second, and had enjoyed a liberal diet as well as the best of hygienic care. There were no dermatologic conditions on either side of the family, and the only sibling was in good health. Both parents had negative serologic tests for syphilis before, during, and after the present pregnancy, and they deny all clinical symptoms of syphilis. Birth was at full term, and the baby, weighing 6½ pounds, appeared entirely normal except for denuded areas on the legs and hands. These were described by the obstetrician as resembling secondary burns.

At the time of admission here the skin was involved by lesions in varying states of maturation. There were distinct thin-walled blebs, measuring up to an inch in diameter, while others apparently had ruptured, leaving moist, collapsed blisters or denuded surfaces. The latter did resemble burns in that the prickle layer was exposed and from it exuded serous fluid. In other areas, especially on the feet and hands, these desquamated zones were undergoing epithelialization, while those regions especially subjected to trauma were crusted and bleeding. There seemed to be no sharply delineated distribution, although the legs and hands were more completely involved than the trunk. A few blebs were present on the diaper area, and scattered blisters were also on the chest, abdomen, and even in the mouth. The "normal" skin was not inflamed or thickened, but blebs could be induced by rubbing with a piece of cotton and these fresh lesions could be changed in contour by pressure—the Nikolsky sign. The remainder of our examination was not revealing; the lungs and heart appeared normal, and there was no enlargement of spleen or liver.

Laboratory data included negative urinalysis, hemoglobin of 17 Gm. per cent, 7,000 white blood cells with a normal differential count, and a positive Mazzini test. This last was checked by a quantitative Kahn determination and a reading of 40 units (1:10) was obtained, but, four days later, the titer was positive at only 2 Kahn units. The Kahn test on cerebrospinal fluid, drawn at the time when the blood test showed 40 units, was also positive. Smears of the fluid aspirated from several blebs showed, in some instances, polymorphonuclear cells and clumps of gram-positive cocci. Unfortunately fluids were not cultured until after instigation of penicillin therapy, but dark-field examinations showed no treponema. Blood cultures did not produce growth. Dr. Evans examined films of the long bones and found no stigma of syphilis.

Therapy has been entirely symptomatic. We have gavaged the feedings because of inability or unwillingness to nurse, and full doses of both sulfadiazine and penicillin have been given. Parenteral fluids and proteins have been administered in amounts sufficient to compensate for losses through the damaged

skin. The lesions themselves have been protected with moist compresses while the uninvolved portions of skin have been exposed to a heat lamp and handling has been kept to a minimum. Nevertheless, the child has continued downhill and new blebs have appeared while many of the older ones have persisted as unhealed surfaces. The temperature remained normal during the first few days but now has risen to between 101° and 103° F., and for the past three days a mild diarrhea has been present.

Fig. 6.—Case 3. Note areas of desquamation on abdomen, blebs on knees, and complete desquamation of inner aspects of feet and legs.

DR. PAUL V. WOOLLEY, JR.—This case is not shown with the idea of exploring completely the mysticisms of dermatologic nomenclature but rather as an example of what I believe is a fairly clear-cut clinical entity which must be differentiated from two similar states calling for specific therapy. The important characteristics in the present case include: (1) The disorder was present at birth; (2) the blebs are easily produced on uninvolved skin by gentle friction; (3) chemotherapy has not modified the course; (4) the site of bleb formation is between the horny layer and the corium; and (5) the prognosis seems far from favorable. There are no associated lesions such as we generally find either with syphilis or sepsis.

Only one of the pediatric or dermatologic texts deals to any comprehensive extent with the bullous diseases of the newborn infant and that is von Ruess'; he reaches no very satisfactory conclusion. Many authors have described similar cases and have tended to append four names rather indiscriminately. *Impetigo congenita* or *neonatorum* is frequently used but is objectionable because the term by definition implies a pyogenic infection. One must not be misled by the finding of cocci in fluid from the blebs; this is a common occurrence in unruptured thermic blisters and merely reflects the rapidity with which a skin

flora is obtained. Another group has been inclined to attach the name of Ritter after the describer of *dermatitis exfoliativa,* but he stressed that the skin in his cases was normal at birth, then became reddened and inflamed, and finally peeled in sheets with bleb formation as a distinctly secondary event. Still other writers use *pemphigus* with such adjectives as *neonatorum, malignant, non-syphilitic,* and *congenita,* an objectionable trend since the modern tendency is to reserve the name *pemphigus* for a specific entity rather than applying it on a morphologic basis. Finally, some regard these cases as *epidermolysis* and add descriptive handles such as *"bullosa congenita."* I personally favor this last as best describing a disease of unknown etiology but characterized by a defect between the horny epithelium and the prickle layer which manifests itself with the formation of bullous collections of fluid.

Regardless of personal etymological preferences it remains important to separate from these cases those actually due to sepsis, more especially, to infection with the staphylococcus. Certainly we can be guided here by three facts: First, there are no other lesions commonly known to occur with staphylococcus infections in the age group; second, there is no response to therapy which is usually specific for the staphylococcus; and finally, a defect is demonstrable in areas where cutaneous effusions do not exist. Syphilis is the other disease entering the differential diagnosis, especially in this case where one serologic test was of appreciable titer. If syphilis produces skin changes of this type it must be most rare since we see roughly fifty fresh cases a year and yet none similar to that of the present baby. Once more I would like to point out that a positive serologic test can mean many things other than syphilis and that we should never be misled but rather should seek confirmatory evidence. In this case we have a repeatedly negative maternal history and serology, there are no visceral or osseous symptoms or findings, and dark-field examinations of the bleb fluids are unproductive. Furthermore, the majority of our congenital syphilities with active lesions respond to penicillin either with a febrile reaction or an increase in serologic titer; this baby has done neither.

Undoubtedly Dr. Zuelzer can comment on the separation of these cases by the pathologist.

DR. WOLF W. ZUELZER (Director of Laboratories and Pathologist-in-Chief).—We have seen several of these cases and have tended to place them as Ritter's disease but with the definite understanding that there is no specific pathologic criterion for so doing. I have not favored the use of the term epidermolysis since this to me refers to a familial disease with manifestations later in life and with a good prognosis. How do you explain the positive cerebrospinal fluid serology? We see many false positive blood reactions but rarely a false spinal fluid test. Was the tap traumatic by any chance?

DR. STERN.—Yes, it contained red cells and an increased amount of protein.

QUESTION.—Do drugs given to the mother ever cause rashes of this type? It seems I have heard it suggested that such skin lesions, often attributed to congenital syphilis, may actually be due to arsenicals received by the mother.

DR. STERN.—This woman was given liver extract injections early in her pregnancy and had castor oil and quinine to induce labor on the day before delivery, but nothing else.

### ADDENDUM TO CASE 3

A final note can be added since this patient died three days after being presented. At autopsy the positive findings were limited to the skin, where varying degrees of separation between the corium and the horny layer were found. There was nothing to suggest syphilis or systemic involvement by the staphylococcus although some sections showed inflammatory changes due to secondary localization within the skin. Dr. Zuelzer once more stressed that the skin lesions do not explain entirely the unsatisfactory outcome and that forces other than those visible microscopically must be operating. No greater unanimity was obtained on nomenclature even after examination of the tissues.

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# Psychologic Aspects of Pediatrics

## THUMB- AND FINGER-SUCKING IN CHILDREN

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MANY ill effects have been attributed to thumb-sucking. It is said to deform the palate and teeth and to lead to air swallowing, oral infection, and gastrointestinal disturbances. It has been looked upon as a habit related to masturbation.

Thumb-sucking may displace the teeth, and it not infrequently causes callous formation on the thumb. Aside from these, the habit is not known to be harmful. It does not cause deformity of the palate, and air swallowing, oral infection, and gastrointestinal disturbances are no more frequent in thumb-sucking children than in others. It is true that thumb-sucking and masturbation are both habitual manipulations of the body which are pleasurable, but there is no reason to believe that they are otherwise related. Moreover, there are no data to indicate that thumb-sucking children masturbate in later childhood more often than other children.

Thumb-sucking is much less often a cause for dental irregularities than is generally believed. According to the studies of Goldberg[1] on uniovular twins, and the serial studies of Sillman,[2] heredity is by far the most important factor determining dental alignment. The teeth in young children may be readily displaced by pressures of various sorts, but, in general, the teeth displaced in this way are readily replaced or resume their original positions spontaneously when the pressures are released.

Since the habit of thumb-sucking disappears, in the large majority of instances, by the sixth year of life, it only rarely leads to irregularity of the permanent teeth.

The habit of thumb-sucking usually becomes established during the early months of life. Occasionally it begins during the teething period and, rarely, even later in imitation of a younger sibling. If the habit persists after 1 year of age, it is likely to run a long course, disappearing between 2 and 5 years of age. It may persist into adult life.

Associated movements frequently accompany thumb-sucking. The child may pull the ear, pat the head, twist or pull the hair, suck a blanket or diaper, rub the cheek or chin with a blanket, pull a blanket in front of the face, etc. The associated movement may persist after the thumb-sucking has ceased.

Though the thumb is the finger generally preferred for sucking, occasionally other fingers are used.

Tongue-sucking is relatively uncommon. It is seen sometimes when the thumb-sucking is prevented by the use of restraints. It also occurs where there

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is macroglossia as in Mongolian idiots and cretins and, occasionally, in healthy infants. The habit is harmless and usually disappears during the second year of life.

Of the hypotheses put forward to explain why children suck their fingers, the one by Levy[3] has received widest attention. On the basis of clinical observations as well as investigations in dogs, calves, and chickens, he concluded that the primary factor causing thumb-sucking is inadequate sucking activity during feeding time. Gesell and Ilg,[4] however, believe that this is only of minor importance. Our experience has been similar. We have frequently seen babies, nursed at the breast and seemingly satisfied in every way, who sucked their thumbs; and we have seen these babies develop later as well-adjusted children.

Throughout life the mouth is used for pleasurable satisfaction. Looked at in this way, thumb-sucking during infancy is no more an undesirable habit than gum-chewing and nail biting in childhood or smoking and munching in adulthood.

Thumb-sucking may cease toward the end of the first year of life, especially when the sucking is associated with feeding, but it often persists. According to Gesell and Ilg[5] it reaches its highest peak between 18 and 21 months of age when some children will sit for hours with thumb in the mouth, either alone or watching other children at play, but not taking part in their activities.

Thumb-sucking is closely associated with sleep, and many children suck the thumb only when falling asleep and during sleep. The 2-year-old child resists removal of the thumb during sleep, the 3-year-old tolerates removal and the 4-year-old spontaneously drops the thumb during sleep.[5]

*Management.*—The parents should be instructed as to the harmlessness of thumb-sucking. The relation of the habit to dental alignment and to the permanent dentition should be explained.

The application of mechanical restraints or bitter tasting substances and adhesive tape to the thumb are to be discouraged. In the first place these devices are unkind. In addition they often rouse the child's negativism and make him resistant. The child may come to suck the thumb in order to attract attention and to annoy the parents.

Censuring, nagging, and shaming should be avoided. They tend to shake the child's faith in himself and make him unsure of parental affection.

Thumb-sucking requires no treatment during infancy or, later on, when it is practiced only in relation to sleep. The handling of the baby should be reviewed with the mother to see that he is held properly during feeding, that he gets an adequate amount of manipulation (but not too much), that the mother knows the baby prefers to be held snugly, not loosely. During early infancy babies may be diverted from sucking the thumb by supplying them with a pacifier. This is a harmless device which can be removed toward the end of the first year without fear of the child's reverting to the thumb.

When thumb-sucking is frequently practiced during the waking hours after the first year of life it means that the child is over-fatigued, bored, or unhappy. Treatment should be directed toward correcting the total situation rather than

the thumb-sucking. The child should have adequate rest and ample play outlets. An attempt should be made to correct undesirable parental attitudes.

By 5 or 6 years of age the large majority of children are ready to drop the habit. Promise of a reward, an appeal to the child's will power or vanity, having the child himself apply a bitter-tasting substance to the thumb or wearing gloves as a reminder is often sufficient to terminate the habit.

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# The Social Aspects of Medicine

## RESPONSIBILITY OF THE PEDIATRICIAN IN THE COMMUNITY HEALTH PROGRAM

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PEDIATRICIANS are becoming increasingly aware of the fact that physical and mental health of children is markedly influenced by social, economic, and other environmental factors. In order, therefore, to promote health effectively, the pediatrician must contribute of his experience to and actively participate in the community organizations that concern themselves with the welfare of children. To this end pediatricians or physicians interested in children and all the agencies dealing with health and welfare in a community should unite their efforts and pool their experiences in an attempt to make the environment suitable, or, as nearly as possible, ideal, for the rearing of children. This may well be looked upon as the health and welfare plan for the community, and should be considered of equal importance with that of the government of a community.

Most directly concerned with health are the practicing physicians, the public health organizations, psychiatrists and psychologists, dentists, nurses, physiotherapists, social service workers, and hospital organizations with their laboratory facilities, technicians, and the like. There are also organizations concerned entirely with some phase of health. As such may be mentioned the tuberculosis association, the cardiac committee, cancer committee, foundation for infantile paralysis, and mental hygiene society. In addition to these there are a number of agencies concerned with other phases of child welfare. The number of these in any given community varies. Some of these agencies are purely local, others are state, and still others are national organizations. Some are public and others are private. Some are concerned almost entirely with health, others are social organizations with health or welfare as one of many interests. Among these may be mentioned the American Red Cross, the American Legion, fraternal orders, and church societies.

It is at the local level that any plan for a coordinated health and welfare program must first be worked out. At this local level physicians are the best qualified persons and the logical guides of the over-all program, although they may do most of their guidance through existing community agencies. The procedure may differ considerably in different places, depending largely upon which organization in the community has developed the greatest leadership and exerts the greatest influence in health work. In general, a procedure organized along the lines suggested below may serve as a guide or model to follow. There is no one way that is necessarily the best or necessarily applicable to every community. The following outline is suggested as one method of procedure:

I. A small committee of five or six members should be formed, representing the main health groups or agencies of the community, such as the county medical society, the pediatricians, if such a group is functioning, the public health organization, the dental association, the visiting nurses association, the tuberculosis association, depending on which agencies are serving the community. This committee may be known as the health council, the coordinating committee, or by a name of its own choice.

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II. This committee should select a volunteer or a paid worker, preferably a health educator, if such is available. The work of this individual should be to canvass the community and make an index or file of all the organizations in that community dealing with youth, as well as the key persons working within each organization. This file should include not only such health agencies as have been mentioned but also all organizations concerned with youth and their welfare such as churches, nursery schools, scouts, YMCA, YWCA, libraries, recreation grounds, movie houses.

III. After the study has been made and the key persons of the community located, representation from a larger group should be sought, and from this larger group should be formed subcommittees along the natural lines on which a community tends to work, namely, committees on (1) handicapped children, (2) mental hygiene, (3) legislation, (4) housing, (5) safety, (6) recreation and entertainment, (7) health education.

IV. The subcommittees may then gather information each in its own field, both of existing programs and contemplated ones. The committee on the handicapped child, for instance, should study the needs of all children with handicaps, not only the obviously crippled but the children with chronic diseases like diabetes, deafness, the visually handicapped. The group interested in mental hygiene should concern itself with facilities for therapy, preventive clinics, custodial care of the feeble-minded, delinquency, and also such factors as minority persecutions and prejudices. A legislative committee may be necessary to influence the building of hospitals or health centers or to obtain full or part-time health officers, public health nurses, etc. Recreation and entertainment committees may include in their programs not only playgrounds but a study of the type of movies the children are seeing, the use made of recreation centers, the care of children of working mothers. The committee on education has limitless possibilities, extending from education for parenthood to combatting prejudice.

V. Meetings of the committees should be held at regular intervals in order to keep information up to date and maintain continuity and interest. The original committee or health council may be expanded to include the chairmen of the subcommittees.

VI. A yearly open conference at which committee reports can be made and needs presented offers a valuable means of educating the community and arousing interest and support. Such a meeting, furthermore, gives excellent opportunity to bring in outside speakers and enlarge the interest of the community.

VII. There are some problems that must be met at a level other than local, for example, the care of the feeble-minded. Such a problem goes beyond the boundaries of the local community. One committee, therefore, should be concerned with cooperation at a county or state level. In this way each community becomes an integral part of the county, state, and eventually the nation.

Large metropolitan areas cannot organize as simply as this. In most large cities there already are in existence a great many agencies and there may also be councils coordinating many of the agencies. These may not wish to be replaced even though they are not representative and new ones may be duplicating existing committees and further confuse the problem. Two suggestions are made to meet the problem in the large cities: First, physicians, particularly pediatricians, should take an active part in the existing councils, giving freely of their experience and advice to various groups. Second, large cities might be divided into communities or sections and the health problems of each section worked out according to the proposed plan or a similar one.

Some of the small communities, and especially those that are relatively new, enlarging, and not too handicapped by tradition, should be able to work out the ideal program and furnish a model to other communities.

In the health and welfare program of his community, the pediatrician, or for that matter every physician, has a distinct responsibility. Regardless of how well he performs his private practice or how busy he is, in a community of free, self-governing people he has a responsibility beyond his private work. The health of the community, the facilities for the care of the handicapped, the custodial care of the mentally deficient, the environmental factors conducive to delinquency, and the health education of the community are a part of his concern. Only by assuming this responsibility in his own field, that of health, can he expect to see the desired progress made. The practical application of scientific knowledge for the welfare of the people cannot lag far behind discovery without creating justifiable dissatisfaction and criticism of our health system.

# Comments on Current Literature

## HEART ARRHYTHMIAS IN CHILDREN

UNTIL recently the heart arrhythmias were regarded as affecting adults almost exclusively, and in studies of these disturbances attention was directed chiefly toward this age group. Consequently, knowledge of arrhythmias in children is still incomplete. Only in rare instances can arrhythmias in children be judged on the basis of experience acquired by a study of thos ein adults. Yet knowledge of disturbances in heart action during early life is of importance with respect to the prophylaxis of heart disease, since different forms of arrhythmias in childhood can remain or recur in later life.

At the heart station of the Crown Princess Lovisa Children's Hospital in Stockholm, 5,600 children under the age of 16 years were examined by electrocardiographic and phonocardiographic methods during the years 1936 to 1946. Pathologic forms of arrhythmia were recorded in 126 children (2.25 per cent). By way of comparison, 200 healthy children were included in order to determine physiologic sinus arrhythmia. A careful analysis of the data accumulated during these extensive studies has been published by Landtman[1] in the form of a monograph, in which the material is presented in sections.

In the section dealing with sinus arrhythmia, Landtman points out that on a statistical basis it appears clear that sinus arrhythmia in children increases with age. Of particular interest is the observation that decreased sinus arrhythmia occurs in children with congenital heart disease (fifty cases) and in children with rheumatic heart affection (fifty cases). The author suggests that the decrease in arrhythmia in these cases may be due to some damage to the sinus node which lessens its sensitivity to external impulses. He concludes that pronounced sinus arrhythmia is indicative of good heart function, while in various heart diseases the reflex mechanism is impeded, resulting in an unusually regular pulse.

Extrasystoles were found in eighty-six cases (1.53 per cent). While this type of arrhythmia is generally regarded as a harmless disturbance in heart action often appearing in clinically healthy children, the survey showed that extrasystoles were relatively more common in children with myocardial damage or heart disease. In general, the ventricular form of extrasystole was more common than the supraventricular; the latter form, however, was noted more frequently in children with pathologic cardiac manifestations.

In the course of these examinations a total of six cases of auricular flutter (0.11 per cent) was recorded. In all these children electrocardiographic studies revealed signs of myocardial damage, confirming the opinion that auricular flutter is a serious condition in children.

In the section concerned with paroxysmal tachycardia, emphasis is given to the fact that while symptoms in older children do not differ markedly from those observed in adults, this disorder in infants presents a clinical picture which differs in many respects (Hubbard[2]). The attack in infants is characterized often by atypical initial symptoms such as anorexia, vomiting, and listlessness. Gradually, however, insufficiency symptoms appear: cyanosis, dyspnea, liver enlargement, and pulmonary congestion. As a rule the duration of these attacks is a matter of hours, but in rare instances an attack may last for several days. While prognosis with respect to health is often good in paroxysmal tachycardia during infancy, there is a definite tendency for the condition to recur. Five cases of paroxysmal tachycardia were observed in the series de-

scribed by Landtman (0.09 per cent). All five children recovered, showing no pathologic signs or symptoms at the latest recorded examination. Apart from the risk of relapse the general prognosis is good, provided no serious heart disease is present. In addition to digitalis and strophanthin, acetylcholine and prostigmine proved valuable medications.

Under conduction disturbances are recorded six cases (0.11 per cent) in which arrhythmia occurred in the form of escaped beats; seven instances of sinoauricular block (0.13 per cent); and nine cases (0.16 per cent) of complete atrioventricular block. Partial atrioventricular block is listed as the most frequent expression of myocardial damage on the basis of infection. Complete atrioventricular block in young people is often congenital, the most common cause of interruption being septal defect.

An interesting section of the monograph deals with heart action in premature infants. Various authors have been interested in the question of whether premature infants show disturbances in heart action to any special extent. Räihä[3] has discussed the possibility that the disturbances result from a temporary lack of oxygen in the capillary system of the heart. Landtman's series included a study of sixty-three premature infants (thirty-one boys, thirty-two girls) under 2 months of age, of whom only ten were more than 1 month old; the weight upon examination averaged less than 2,500 Gm. Pathologic changes in these sixty-three premature children were not marked. In three premature infants, small notchings in the QRS complexes were noted; in one there were slightly elevated S-T segments in leads II and III. Extrasystoles of supraventricular origin were recorded in one child. Phonocardiographic examinations were made in forty-eight of the sixty-three infants, and in only one case was there an organically conditioned murmur registered. Thus, apart from relative tachycardia, which often distinguishes heart action in premature children during the earliest period of life, the studies did not reveal by electrocardiogram any special disturbances characterizing heart action in premature infants.

TABLE 15 (FROM LANDTMAN). PATHOLOGIC ARRHYTHMIAS DETECTED IN MATERIAL COMPRISING 5,600 CHILDREN UNDER THE AGE OF 16 YEARS

| ARRHYTHMIA | | NO. CASES | FREQUENCY (%) |
|---|---|---|---|
| *Disturbances in the stimulus formation* | Extrasystoles | 86 | 1.53 |
| | Auricular flutter | 6 | 0.11 |
| | Paroxysmal tachycardia | 5 | 0.09 |
| *Conduction disturbances* | Escaped beats | 6 | 0.11 |
| | Sinoauricular block | 7 | 0.12 |
| | Partial auriculoventricular block | 5 | 0.09 |
| | Complete auriculoventricular block | 9 | 0.16 |
| | Complicated arrhythmias | 2 | 0.04 |
| | Totals | 126 | 2.25 |

A summary of data presented in Landtman's monograph is given in the accompanying table. The author includes in each section of the monograph a brief review of pertinent data presented by authorities in the field. The bibliography is an extensive one, embracing international literature. This monograph constitutes a clear, authoritative presentation of difficult subject matter.

RUSSELL J. BLATTNER.

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# Correspondence

Cambridge, Mass.,
September 21, 1947

To the Editor:
My dear Dr. Veeder:

I should like to draw the attention of psychiatrists in general, and Dr. Weinfeld in particular (author of a recent article on the self-demand feeding schedule), to a few practical considerations which I have yet to see in print.

The advocates of the self-demand feeding schedule never adequately define their terms. As babies cannot talk and thus make their wishes clearly understood, the demand undoubtedly refers to crying. But whether the baby is crying from hunger or for some other reason is largely guesswork on the part of the mother. After a mother has run downstairs and heated a bottle half a dozen times only to find that the baby has gone off to sleep when she gets back upstairs, she will decide to wait until the baby has cried a certain length of time before she makes the next trip. How long a period of crying constitutes a demand for feeding? This problem is even more confusing when the mother is breast feeding, for when the baby cries only one or two hours after the last feeding the mother is likely to feel quite sure that she has nothing more to offer the baby for quite a while.

What about the baby that is fat and happy and quietly chuckles to itself in the crib for one or two hours in the morning? Must the mother wait until the baby cries before she feeds him? My 5-month-old daughter is of this variety. She has been on three meals a day since 3 months of age. She practically never cries. The other day when I was away and she was left in charge of her father, she did not cry for lunch until 3 P.M. So why not just feed her at 3 P.M.? The psychiatrists forget my other two children who are counting on my taking them to the beach at that time. Also, that feeding postpones her supper indefinitely and I am counting on a good night's sleep and want to feel sure that my baby is fed before I go to bed. Must I wait until she cries for supper?

Dr. Weinfeld agrees that the 3-year-old may wait happily for a routine feeding where a 6-week-old infant will not. True, but he does not make any reference to the intermediate ages or at what age a pediatrician should advocate a routine. I have found it safe to tell mothers that somewhere between 6 weeks and 3 months of age the average baby will adapt happily to a routine. If the psychiatrists would agree to some such early age of transition to a routine schedule, at least half their quarrel with pediatricians would be resolved.

Finally, if, as Dr. Weinfeld says (J. PEDIAT. 31: 204, 1947), speaking of the neonatal period, "Physical activity at this time is at an infracortical level and the responses are purely reflex in character," why are the psychiatrists so concerned about the psychogenic effects of what takes place at this period? So, if in the first 6 weeks to 2 months of age it does not matter, and shortly thereafter the baby adapts happily to a routine, it would seem that the pediatricians have done no great harm, while the psychiatrists are sending a bevy of mothers into a flurry of warming bottles only to have them go cold again, ignoring their other children to wait on the cry of their youngest, to say nothing of having them find themselves in a constant state of indecision, certainly not a trait to encourage in a young mother.

Yours truly,

(Signed) PATRICIA WANNING

Dr. Wanning's letter was submitted by the Editor to Dr. Weinfeld, who replied as follows:

Chicago, Ill.,
October 20, 1947

Dear Dr. Veeder:

Several pediatricians have written me, since the publication of my paper, raising the same questions and objections that Dr. Wanning writes about. Many of the pediatricians attending the Pittsburgh meeting of the Academy where my paper was read were similarly opposed to the employment of a self-demand routine. This has greatly impressed me, because in more than fifteen years of private practice in pediatrics I have found that only a very few mothers, with the exception of those whose babies were "colicky," have had difficulty in determining when their infants want or need to be fed. Dr. Aldrich reports similar experience in Rochester, Minn. (A Self-Regulating Feeding Program for Infants, J.A.M.A. 135: 341, 1947): "In the majority of instances mothers were surprised when they were asked if they had trouble knowing when their babies were hungry." I suspect that the relatively greater resistance to this program by pediatricians rather than by mothers is because of the simplicity of giving instructions for a fixed feeding routine. It is admittedly more difficult and time-consuming to explain to a mother objective signs of hunger, the rationale of indulgence and self-regulation, and to reassure her that she will quickly learn the meaning of her baby's behavior.

Some of the specific questions Dr. Wanning raises cannot be answered categorically. The meaning of the cry, the length of crying permitted before being fed has to be left to the judgment of the mother.

Through her own infant's feeding behavior, Dr. Wanning answers her own question concerning the satisfied baby who is "fat and happy and quietly chuckles" for long periods. "Must the mother wait until he cries before she feeds him?" The answer to this is that older infants who have been satisfied in early infancy have learned to wait and have other means of showing their hunger. In addition they have demonstrated just as Dr. Wanning's daughter did that they were ready for three meals a day. Here certainly is an excellent example of self-regulation. Of course, in these older infants it would be absurd and psychologically unsound to wait until they cried before being fed. That would be habit training at its poorest. One of the greatest virtues about self-demand feeding is that eating becomes associated with pleasure and not with pain or crying.

I agree with Dr. Wanning that somewhere "between 6 weeks and 3 months of age the average baby will adapt happily to a routine." Dr. Aldrich's factual observations also confirm this. There should not be, and, as far as I know, there is no quarrel between psychiatrists and pediatricians on this point except for those pediatricians who continue to practice arbitrary dogmatic medicine, ignoring the different individual endowments and needs of each infant.

Dr. Wanning misinterprets my comments on the neonatal period when physical activity is at an infracortical level. Of course no one can say that control emerges at any given moment, or in any given quantity. Psychiatrists make no such contention that "the first 6 weeks to 2 months of age does not matter." As a matter of fact, quite the opposite is true. A. Freud (Psychoanalytic Study of the Child, Vol. II, p. 124, International University Press, 1946) writes, "The newborn infant is self-centered and self-sufficient as a being when he is not in a state of tension. When he is under the pressure of urgent bodily needs, as, for instance, hunger, he periodically establishes connections with the environment which are withdrawn again after the needs have been satisfied and the tension is relieved. These occasions are the child's first introduction to experiences of wish-fulfilment and pleasure. They establish centers of interest to which libidinal energy becomes attached. An infant who feeds successfully 'loves' the experience of feeding."

Finally, in answer to Dr. Wanning's concluding paragraph, I quote from a previous paper (Gustave F. Weinfeld: Pediatric Approaches in Infancy, Am. J. Orthopsych. 11: 423, 1941): "In the last analysis it is the responsibility of the parent to execute whatever feeding program is recommended. Under certain circumstances a flexible program may be presented in such a way that it becomes an inflexible tool in the mother's hands. . . . When,

for example, many domestic demands are made upon a mother, some degree of regularity in feeding her infant is essential for her equanimity. Under such conditions a regular feeding schedule might be preferable, but it should be employed as a servant and never as a master, and the infant will be spared anxiety that might have arisen from an environment crowded with confusion due to the unpredictability of the feeding periods.''

Very truly yours,

(Signed) GUSTAVE F. WEINFELD, M.D.

Because of Dr. Aldrich's interest in the subject, and in view of his recent paper in *The Journal of the American Medical Association*, Dr. Wanning's letter was submitted to him for comment.

Dear Dr. Veeder:

This letter from Dr. Wanning brings up a few points about which I am glad to comment.

In the first place, it has always seemed to me unfortunate that the term ''self-demand'' was ever used, because it really does imply furious crying and autocratic behavior on the part of the infant. Opposed to this term is what I consider a better one, ''self-regulating,'' which implies a more lawful signaling of need on his part.

As we apply the principle of self-regulating in Rochester, we simply advise each mother to watch her baby's behavior for a few days or weeks to find out his hunger rhythm. Is he a two, three, or four-hour baby? Once his innate feeding intervals have been established, it becomes a simple matter for the mother to adjust the actual hours of feeding to the household routine. In our experience, self-regulation leads to feeding habits of great regularity in 98 per cent of babies by the end of the first month. Therefore, it is not really a queston of regularity or irregularly but one of *whose* regularity.

Furthermore, I am sure that neither Dr. Weinfeld nor any other pediatrician advocating this method would think of turning all these babies loose without pediatric control, by which I mean the application of our skill to the care of all babies, including those who are aberrant. Those with colic, for instance, will need special attention and management. The fact that we are willing to adjust our techniques to the individual hunger rhythms of babies does not mean that we have to throw the use of our brains and experience ''out the window.'' It probably requires the use of more rather than less cerebral energy to apply what we know of normal infant behavior to our supervision of newborn as well as older infants. But that is our function: to provide the ''know how'' and perspective to mothers who are eager to learn and who are, I am convinced, trying to do a good job. Neither a rigid routine, a self-demand or a self-regulating system will succeed in this day and age without wise counsel from an experienced source.

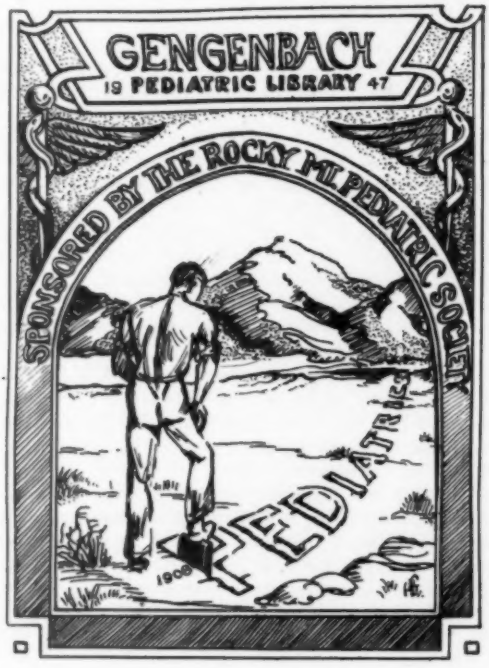
It should be added that our experience here with many hundreds of babies, all on a self-regulating regimen, has been that very few mothers become confused. In fact, they express great surprise when asked if they have difficulty in determining when their babies are hungry. The question usually is met with a remark to the effect that we ''doctors don't always understand the ways a mother has of knowing about her own baby.''

(Signed) C. A. ALDRICH.

# News and Notes

The meeting of the **Chicago Pediatric Society** on Dec. 16, 1947, honored the eightieth birthday of Dr. Isaac A. Abt (December 18). Dr. Abraham A. Levinson discussed Dr. Abt's contribution to pediatrics, and Dr. Julius H. Hess, Dr. Isaac Abt—the person. Dr. H. William Elghammer presented Dr. Abt with a scroll from the **Chicago Pediatric Society.**

On Oct. 18, 1947, the **Rocky Mountain Pediatric Society** gave a dinner in honor of Dr. F. P. Gengenbach, the first professor of pediatrics at the University of Colorado and one of the founders of the Rocky Mountain Pediatric Society in 1920. At the dinner a library, the Gengenbach Pediatric Library, was presented to the medical school by Dr. Wiley Jones. The library will be housed adjacent to the pediatric ward.




Dr. Harold B. Cushing, emeritus professor of pediatrics at McGill University died in Montreal on Oct. 31, 1947. Dr. Cushing was one of the pioneer Canadian pediatricians, and it was largely through his efforts that pediatrics became an independent specialty at McGill.

Dr. Henry Heiman of New York City died Nov. 19, 1947. He was on the pediatric staff of Mt. Sinai Hospital as chief and consultant for fifty-eight years.

The **Texas Pediatric Society** has elected the following officers for 1947-1948:
President: Charles B. Alexander, San Antonio
President-elect: John K. Glen, Houston
Secretary: John Ashby, Dallas
Treasurer: W. M. Bradford, Dallas

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Several short two-day postgraduate courses in pediatrics will be given by Washington University at the St. Louis Children's Hospital. The dates and subjects are as follows:

Jan. 26 and 27, 1948—Commoner Diseases of the Blood and Blood-Forming Organs. Dr. Louis K. Diamond of Boston will be a guest speaker on the staff of instruction.

Feb. 16 and 17, 1948—Nephritis and Other Genitourinary Diseases.

March 15 and 16, 1948—Fluid Administration and Electrolyte Balance.

Detailed information may be obtained from the Director of Postgraduate Studies, Washington University Medical School, St. Louis 10, Mo.

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Dr. John A. Lichty of Rochester, N. Y., has been appointed assistant professor of pediatrics at the University of Colorado Medical Center. His primary responsibility will be that of pediatric consultant to the Colorado State Department of Health, and he will be in charge of the postgraduate education program in pediatrics at the University of Colorado and the State Health Department.

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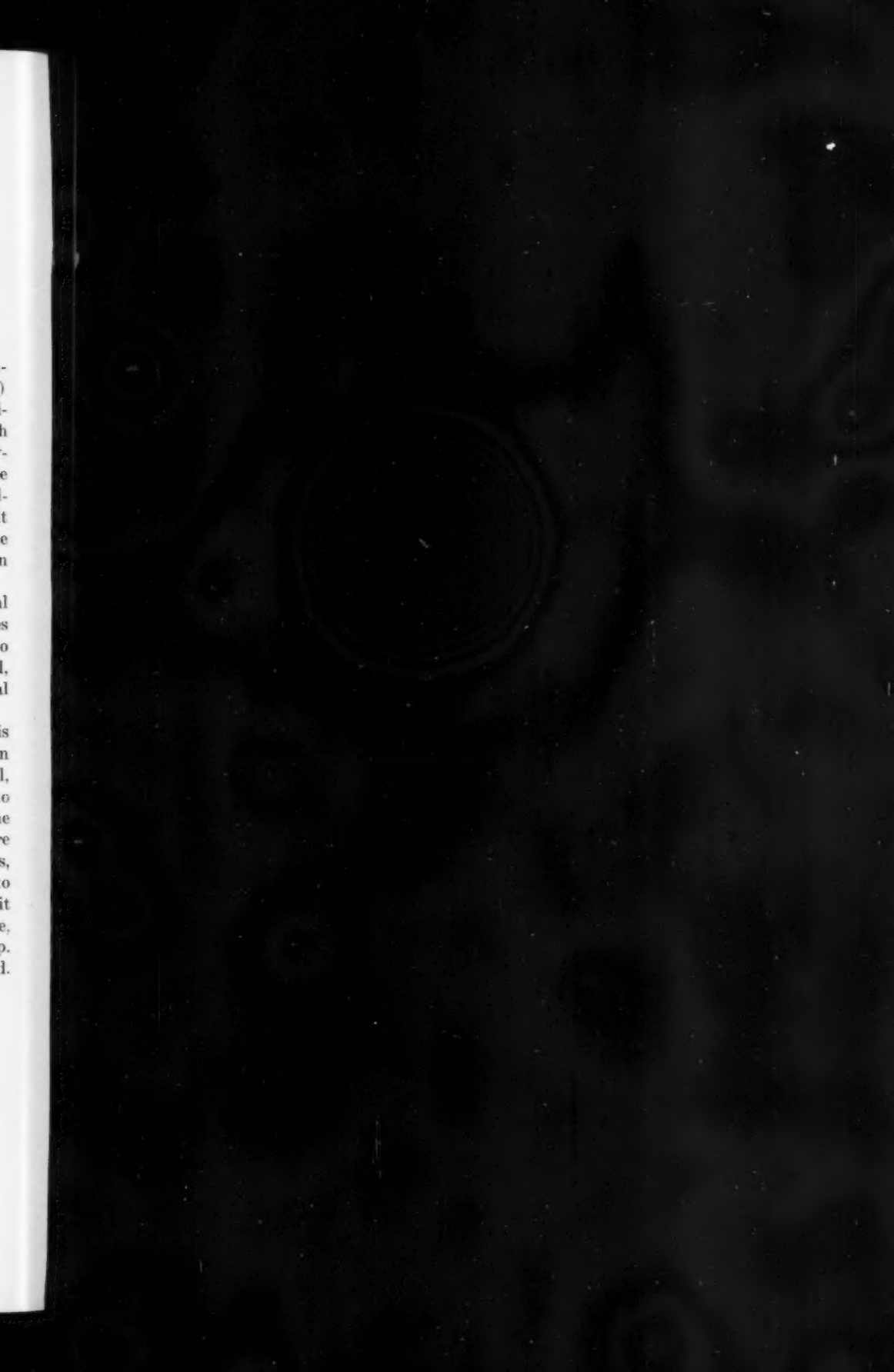
Dr. Tyree C. Wyatt has been appointed professor of pediatrics and chairman of the pediatric department of Syracuse University College of Medicine at Syracuse, N. Y. He received his M.D. degree from Syracuse University in 1922. From 1922 to 1927 he was connected with the department of pathology at Syracuse. This was followed by appointments at Peter Bent Brigham Hospital, Boston, and New York Nursery and Child's Hospital and Cornell University pediatric department, New York. In addition to his new duties he will continue to direct the pediatric pathology at Syracuse Memorial Hospital.

# Editor's Column

## THE PHYSICIAN AND THE COMMUNITY

THE plea for more active participation and leadership by physicians in community affairs made by Dr. Thelander in this month's Journal (p. 102) goes to the very root of some of the social problems confronting American medicine. Nearly every community problem has a health aspect or angle which needs intelligent medical guidance. The failure on the part of so many physicians to interest themselves in the social problems of the community turns the leadership over to social workers and other lay persons who do not have knowledge and understanding of the medical aspects, and this in turn makes it difficult to explain or discuss the complex problems of medical care now facing the medical profession without being open to the charge of self-interest rather than the interest of the community.

As a whole the pediatricians have participated in meeting community social problems more than any other medical group, and the names of many colleagues who have given freely of their time and knowledge to the community come to mind. The very nature of the pediatrician's work, the health of the child, makes his participation in community social activities imperative if the goal of pediatrics is to be accomplished.

The common excuse given by the average physician is lack of time. It is noticeable, however, that the busier the physician, the more he participates in community activities. The constantly increasing number of hospital staff, local, sectional, and specialty medical meetings where medical men get together to discuss the purely technical side of their profession has been overdone, with the result that there are too many medical meetings. If a part of this time were spent by the doctor in working with lay groups in meeting community problems, not only would more be accomplished, but it would be of the greatest service to the medical profession by putting it in a better position in the community than it holds at the present time. While the physician as an individual is, as a rule, held in the highest respect, this can hardly be said for physicians as a group. Dr. Thelander gives one of the reasons and points out how it can be corrected.

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